Evidence of being cured for nasopharyngeal carcinoma: results of a multicenter patient-based study in China

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Summary

Background The survival rates of patients with nasopharyngeal carcinoma (NPC) have improved significantly, but there is no consensus on whether they can be considered cured. We aimed to determine whether a statistical cure could be achieved for patients with NPC in the contemporary therapeutic landscape.

Methods This retrospective multicenter study enrolled 6315 patients with nonmetastatic NPC from nonendemic and endemic regions of China from 2007 to 2020. We applied mixture and nonmixture cure models to estimate the cure probabilities and cure times by incorporating background mortality for the general population, matching by gender, age, and diagnosed year.

Findings With death as the uncured event, the probability of patients with NPC achieving a life expectancy at par with the general population was 78.1%. Considering progression as the uncured event, the likelihood of patients attaining a life expectancy without progression equivalent to that of the general population was 72.4%. For individuals, the probabilities of achieving cure were conditional and time-dependent, requiring approximately 7.1 and 4.7 years with 95% certainty, respectively. The corresponding cure times for uncured patients were 8.9 and 6.8 years, respectively. The cure probability was correlated with age, Eastern Cooperative Oncology Group score, TNM staging, Epstein–Barr virus DNA copies, and lactate dehydrogenase. The correlation was excellent between 5-year overall survival/progression-free survival and cure fractions.

Interpretation Statistical cure is potentially achievable among patients with NPC undergoing contemporary treatment modalities. The results hold significant potential implications for both clinical practice and patient perspectives.

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Keywords: Nasopharyngeal carcinoma; Cure model; Cure fraction; Relative survival; Patient consultation; Study design

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Research in context

Evidence before this study

The survival rates of patients with nasopharyngeal carcinoma (NPC) have improved. Nevertheless, the curability of NPC and the cure probability remain unexplored in the contemporary therapeutic landscape. We searched PubMed up to March 13, 2024, with no language restrictions, using the terms ("prognosis") AND ("nasopharyngeal carcinoma") AND ("model"). The search yielded 3680 articles, of which 673 reported the development of a survival prediction system. Among these, none developed a cure model in extensive cohort of patients with NPC receiving modern treatment modalities.

Added value of this study

By using cure models incorporating background mortality for the general population, in 6315 patients with nonmetastatic NPC in multiple representative tertiary centers from endemic and nonendemic regions of China, we found the cure was achieved across most risk-stratified subgroups of patients with NPC. With death and progression as the uncured events, the probability of cure for patients with NPC was 78.1% and 74.1%, respectively. For individuals, the probabilities of achieving cure were conditional and time-dependent, requiring approximately 7.1 and 4.7 years with 95% certainty, respectively. The correlation was excellent between 5-year overall survival/progression-free survival and cure fractions.

Implications of all the available evidence

This large-scale comprehensive study determined that despite significant heterogeneity in NPC, the concept of cure remained valid and reliable regardless of pretreatment characteristics. These outcomes could help enhance clinical management, patient consultations, and clinical trials designs related to NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a relatively rare cancer worldwide, predominantly prevalent in East and Southeast Asia.[1] The substantial heterogeneity of NPC leads to diverse prognoses among patients with the same stage.[2] Due to advancements in treatments, better handling of toxicity, and more rational screening programs, the survival rates of patients with NPC have improved.[3,4] However, the survival outcomes for individuals with advanced-stage or high-risk diseases did not significant improve and remained unfavorable.[5]

In our previous study on the survival probability of patients with NPC, a risk-dependent increase was found over time post-radiotherapy.[6] In the first 4 years after treatment, the annual incidence of mortality and progression peaked at 5.5% and 10.7%, respectively, and declined thereafter. In another recent study,[7] conditional locoregional recurrence-free survival and distant metastasis-free survival gradually increased with prolonged survival time, accompanied by annual risk reduction of locoregional recurrence and distant metastases. In light of these long-term trends, it is plausible to consider whether NPC could be classified as a curable condition with contemporary therapeutic strategies.

Despite the challenges of determining a cure at the individual level in epidemiology, at the population level, patients receiving specific treatment are considered cured when the mortality (hazard) rate of the diseased cohort returns to the expected level of the general population matched for age, gender, and diagnosed year without the disease. From an analytical perspective, statistical cure is achieved when the expected mortality (hazard) rate attributed to a primary disease or secondary complication is equal to zero, resulting in the plateauing of the relative survival (RS) curve.

Cure models represent a special type of survival analysis model well suited for quantifying long-term survival. It is assumed that there is a certain proportion of patients will never succumb to or progress due to the treated disease.[8] By using this conceptual model, the curability of colon cancer,[9] hepatocellular carcinoma,[10,11] and non-Hodgkin or Hodgkin lymphoma have been verified.[12,13] Conversely, diffuse large B-cell lymphoma[14] and breast cancer[15] may lack an inherent curative potential. Nevertheless, the curability of NPC and the cure probability remain unexplored within the framework of contemporary therapeutic modalities.

We aimed to determine the cure probability of NPC by using data from an extensive cohort of patients with NPC in multiple representative tertiary centers, including endemic and nonendemic regions of NPC from North, Central, Southwest, and South China. The present study modeled the statistical cure in two scenarios (one using death as the uncured event vs. one using both progression and death as uncured event). With overall death as the uncured event, cure occurs when patients have an equal likelihood of survival, regardless of tumor progression, as the general population. With progression as the uncured event, cure occurs when patients have an equal likelihood of survival without tumor progression as the general population. The general population is defined as individuals without NPC matched for age, sex, and year of diagnosis.

Methods

Study population

Between January 2007 and December 2020, we retrospectively reviewed 6782 patients with nonmetastatic NPC from four tertiary cancer centers in China. We

included patients treated with intensity-modulated radiation therapy (IMRT) and those with complete baseline characteristics. Accordingly, we excluded patients who received conventional radiation therapy (such as 2D or 3D radiation therapy techniques), or had incomplete baseline clinical data. Consequently, the final dataset consisted of 3052 patients from the nonendemic region (National Cancer Center cohort, Beijing, North China) and 3263 from the endemic regions, including 1996, 717, and 550 from Guangzhou (South China), Sichuan (Southwest China), and Hunan (Central China), respectively. Supplementary Figure S1 shows a detailed illustration of the patient selection. We systematically collected patients' clinical and demographic characteristics. The study received approval from the Institutional Review Board, which waived the necessity for informed consent (Approval No. 23/353-4095).

Treatment and follow-up
All enrolled patients were treated with radical IMRT, with radiation dosage ranging from 2.0 to 2.27 Gy per fraction, delivered five times weekly for 6–7 weeks. Cumulative doses >66 Gy were targeted for primary tumors and metastatic lymph nodes; doses ≥50 Gy were applied to potential infiltration sites. The selection and duration of the chemotherapy, including the induction, concurrent, and adjuvant phases, were at the discretion of the treating clinician, with a predominant utilization of platinum-based agents.

We conducted systematic evaluations at 3-month intervals during the first 2 years, and semi-annual assessments for the next 3–5 years, followed by subsequent annual examinations.

Survival endpoints
Statistical cure is first modeled with overall death as the uncured event. However, NPC is a chronic condition necessitating continuous therapeutic strategies, and advancements in therapies targeting NPC progression may lead to extended survival post-tumor progression. Additionally, previous studies have shown that defining patients with tumor recurrence or metastasis as cured even if they are alive is inappropriate, and using progression as the uncured event for modeling cure is superior to overall death.[10,11,16] Hence, we also investigated progression (including death of any cause, tumor recurrence, and metastasis) as the uncured event in the cure model. With overall death as the uncured event, the cure fraction was analyzed to examine the probability of attaining a survival rate comparable to that of the general population. With progression as the uncured event, the cure fraction was analyzed to estimate the likelihood of achieving a survival probability without tumor progression equivalent to that of the general population. For instance, if cure is defined solely as being alive (with death as the uncured event), a patient who survives despite disease recurrence would be considered cured;

however, if cure is defined as being alive without disease progression (with progression as the uncured event), a patient would not be considered cured. Overall survival (OS) was defined as the timeframe from treatment initiation until death from any cause or the last follow-up visit. Additionally, progression-free survival (PFS) was defined as the duration from treatment initiation to death from any cause, tumor recurrence, metastasis, or the last follow-up.

Relative survival
We estimated the expected survival in the general population during an event (mortality or progression) by using population survival tables from the China National Bureau of Statistics, which provided matches for age, gender, and year of diagnosis. RS was computed as the ratio of observed to expected survival in the general Chinese population, which was matched for age, sex, and year of diagnosis by using the Ederer II method.[17] Curability was confirmed when surviving patients exhibited mortality rates comparable to those of the general population.

Cure model
A fundamental prerequisite for the application of the cure model is its statistical validity.[8] If a subset of patients who do not experience disease progression or mortality exists, the survival curve will exhibit a flattening trend on the y-axis, suggesting the occurrence of a cure within a reasonable timeframe.[8,18] Therefore, the validity of the assumption was verified through the assessment of the OS and PFS curves as well as the RS curves. Supplementary Figure S2a and b showed that both OS and PFS curves tended to plateau during follow-up. Fig. 1a–b showed that RS curves tended to flatten during follow-up. These indicated that using death and progression as the events of cure model did not violate the assumption, making the cure hypothesis acceptable.

With progression as the uncured event, we used the nonmixture model due to its theoretical basis in modeling tumor progression post-treatment.[18,19] With death as the uncured event, we used a mixture model as recommended by the developers of this methodology.[19]

The cure fraction is a useful measure for gauging the probability of achieving success with a therapeutic intervention. With death as the uncured event, the cure fraction was defined as the proportion of subjects who would never die from NPC. With progression as the uncured event, the cure fraction was defined as the proportion of subjects who would never have NPC progression. Cure fractions were estimated using parametric modeling and a logit link function.[18]

Cure time, i.e., time to cure, is defined as the interval from the initiation of treatment to the point at which excess mortality (hazard) reaches zero, indicating that the population is statistically cured.[18] As previously
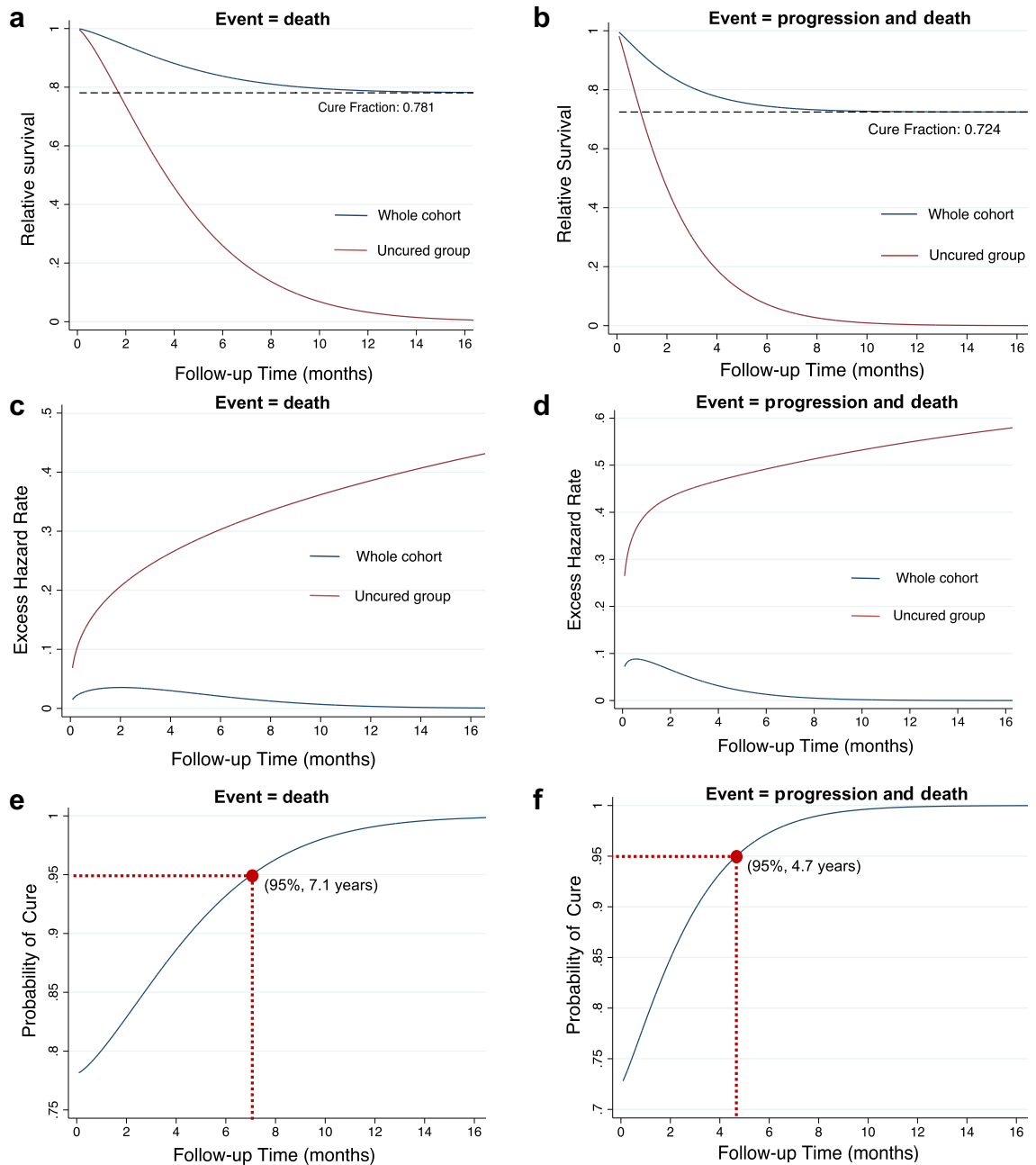
Fig. 1: Cure model results. (a) Predicted relative survival (RS) curves of the entire patient cohort (blue line) and uncured patients (red line) by using the mixture cure model with death as the uncured event. In the entire group, the RS curve plateaus a at 78.1%, representing the cure fraction (dashed line). The figure indicates that the probability patients with NPC achieving the same life expectancy as the matched general population was 78.1%. (b) Predicted RS curves of the entire patient cohort (blue line) and uncured patients (red line) using the nonmixture cure model with progression as the uncured event. Among the entire group, the RS curve plateaus at 72.4%, representing the cure fraction (dashed line). The figure indicates that the probability of patients with NPC achieving the same life expectancy and tumor-free as the matched general population. (c) The excess hazard rate of the entire cohort (blue line) and uncured patients (red line). Excess hazard continuously decreased in the entire cohort until it approached zero at 8.9 years after treatment. Conversely, excess hazard progressively increased over time in the uncured patients. (d) The excess hazard rate of the entire cohort (blue line) and uncured patients (red line). Excess hazard continuously decreased in the entire cohort until it approached zero at 6.8 years after treatment. Conversely, the excess hazard progressively increased over time in the uncured patients. (e) The conditional probability of achieving a cure over time with death as the uncured event. The likelihood of being cured was approximately 82% if a patient was alive 2 years after treatment. Over time, the likelihood increases, reaching 95% at 7.1 years.

proposed, the cure time can be calculated as the moment when the vast majority of uncured patients have died.[20] In the present study, we defined the cure time as the moment when 95% of the uncured patients would have died. The 95% threshold was regarded as clinically relevant. After this time, the excess mortality (hazard) associated with NPC becomes statistically negligible. At the individual level, the required survival time for patients with a 95% probability of cure was also computed.

Statistical analysis

The number of cases and percentages were used to report categorical variables, while continuous variables were presented as medians and ranges. Continuous variables were categorized based on widely recognized cutoff values. Previous studies have shown that the cutoff values for Epstein–Barr virus (EBV) DNA load (2000 and 20,000 copies/mL),[21,22] and lactate dehydrogenase (LDH, 245 U/L)[23,24] have substantial prognostic value. Survival estimates were generated using the Kaplan–Meier method. Nonmixture and mixture cure models were fitted using the strsmix and strsnmix algorithms in STATA/SE 16.0 (STATA, College Station, TX, USA), respectively.[25] The cure fraction was compared using the chi-square test. All statistical analyses were two-tailed, with a type I error rate of 5%.

In the additional sensitivity analysis, the association between distributions of survival rates and cure fractions was investigated using linear regression analysis in R 4.2.0 (http://www.r-project.org/) based on subgroups derived from predefined and wide-accepted prognostic factors. The relationships between the OS/PFS rates and cure fractions were evaluated at additional landmark time points, specifically at 12, 36, 60, and 84 months. Squared linear correlation (R^2) was computed to compare the association between OS/PFS rates at different time points and cure fractions by generating corresponding values within distinct subgroups. An R^2 value approaching 1 indicated a stronger correlation. Based on previous studies,[26,27] R^2 was evaluated as excellent if it surpassed 0.9, very good if it exceeded 0.75, good if it was above 0.5, moderate if it surpassed 0.25, and poor otherwise.

Role of the funding source

The funder of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the report.

Results
Patient characteristics and survival outcomes

Table 1 shows the baseline clinical characteristics of the 6315 enrolled patients. Most patients were aged between 30 and 59 years, accounting for >75% of the entire population. Most tumors were locally advanced disease (85.6%). Approximately half of the patients received concurrent chemoradiotherapy (CCRT) (44.9%), and approximately one-quarter of patients received introduction chemotherapy (IC) followed by CCRT (IC + CCRT, 25.2%) or IMRT alone (21.1%). Moreover, less than 5% of patients received IC followed by IMRT (IC + IMRT), CCRT followed by adjuvant chemotherapy (CCRT + AC), IC + CCRT + AC, IMRT + AC or IC + IMRT + AC. During a median follow-up period of 77 months (range, 6–204), 1548 (24.5%) patients had tumor progressions and 1006 (15.9%) died. The OS rates at 5 and 10 years were 82.7% and 73.3%, respectively, with the corresponding PFS rates of 74.6% and 66.1%, respectively.

Relative survival

With death as the uncured event, the RS rates for all enrolled patients at 5 and 10 years were 87.6% [95% confidence interval (CI), 86.4%–88.7%] and 84.2% (95% CI, 82.0%–86.4%), respectively (Fig. 1a). With progression as the uncured event, the RS rates for all enrolled patients at 5 and 10 years were 79.0% (95% CI: 77.7%–80.2%) and 75.9% (95% CI: 73.8%–78.0%), respectively (Fig. 1b). The RS curves plateaued within the 10-year follow-up across the entire cohort, as well as in most of the risk-stratified subsets (Fig. 1a and b; Fig. 2a–p), suggesting the statistical feasibility of a cure for NPC.

With death as the uncured event, the maximum excess hazard rate for the whole cohort reached 3.5% within the second year, followed by a continuous decline (Fig. 1c). With progression as the uncured event, the maximum excess hazard rate for the whole cohort reached 8.8% within the first year, which decreased thereafter until it approached zero (Fig. 1d).

Cure fraction

The cure models achieved convergence and excellent fit for NPC across the whole cohort and its subsets. With death as the uncured event, the cure model indicated that the likelihood of patients with NPC achieving a life expectancy at par with the general population was 78.1% (95% CI, 75.3%–80.6%; Fig. 1a). With progression as the uncured event, the likelihood of patients attaining a life expectancy without progression equivalent to that of the general population decreased to 72.4% (95% CI, 70.7%–74.1%; Fig. 1b). For individuals, the probabilities of achieving cure were conditional and time-dependent (Fig. 1e–f). A patient who survives for 2 years post-treatment has an 82% probability of being considered cured (with death as the uncured event), which increases

(f) The conditional probability of achieving a cure over time with progression as the uncured event. The likelihood of being cured was approximately 84.9% if a patient was alive without tumor progression 2 years after treatment. Over time, the likelihood increases, reaching 95% at 4.7 years. PFS, progression-free survival; OS, overall survival; RS, relative survival.

Characteristics	Number of patients (%)
Year of diagnosis	
2007–2010	966 (15.3)
2011–2015	2665 (42.2)
2016–2020	2684 (42.5)
Sex	
Male	4685 (74.2)
Female	1630 (25.8)
Age, years (median, range)	47 (9, 96)
<18	130 (2.1)
18–29	385 (6.1)
30–39	1149 (18.2)
40–49	1973 (31.2)
50–59	1652 (26.2)
60–69	816 (12.9)
>70	210 (3.3)
ECOG score	
0	2510 (39.7)
1	3698 (58.6)
2	107 (1.7)
Histological type	
Nonkeratinizing	6127 (97.0)
Keratinizing	188 (3.0)
AJCC 8th T stage	
T1	816 (12.9)
T2	1017 (16.1)
T3	2885 (45.7)
T4	1597 (25.3)
AJCC 8th N stage	
N0	744 (11.8)
N1	2189 (34.7)
N2	2404 (38.1)
N3	978 (15.4)
AJCC 8th clinical stage	
I-II	911 (14.4)
III	3045 (48.2)
IVA	2359 (37.4)
EBV DNA (copies/mL)	
Median (range)	159 (0, 4×10^9)
LDH (U/L)	
Median (range)	157 (0, 758)
Treatment modality	
CCRT	2835 (44.9)
IMRT	1333 (21.1)
IC + CCRT	1594 (25.2)
IC + IMRT	234 (3.7)
CCRT + AC	135 (2.1)
IC + CCRT + AC	145 (2.3)
IMRT + AC	13 (0.2)
IC + IMRT + AC	26 (0.4)

(Table 1 continued on next column)

Characteristics	Number of patients (%)
(Continued from previous column)	
Regions	
Beijing	3052 (48.3)
Guangzhou	1996 (31.6)
Sichuan	717 (11.4)
Hunan	550 (8.7)

Abbreviations: AC, adjuvant chemotherapy; AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group; IC, induction chemotherapy; IMRT, intensity-modulated radiation therapy; LDH, lactate dehydrogenase; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival.

Table 1: Clinical characteristics of the enrolled 6315 patients with nonmetastatic NPC.

over time, reaching 95% at 7.1 years (95% CI, 5.6–8.9 years; Fig. 1e). Thus, to achieve a 95% probability of being cured (with death as the uncured event), the required survival time for a patient was 7.1 years. Similarly, a patient who survives without tumor progression for 2 years post-treatment has a probability of 84.9% of being considered cured (with progression as the uncured event), which gradually increases, reaching 95% at 4.7 years (95% CI, 4.1–5.4 years; Fig. 1f). Thus, the required survival time to achieve a 95% probability of cure, with progression as the uncured event, is 4.7 years.

Cure fraction and prognostic factors
Table 2 presents the cure fractions categorized by risk factors with death and progression as the events, respectively. With death as the uncured event, the univariate analysis revealed that the significant determinants of cure probabilities included age, ECOG score, TNM staging, EBV DNA copies, and LDH (all $Ps < 0.05$). The same findings were observed when using progression as the uncured event. For patients aged 18–69 years, cure fractions were relatively high and stable, whereas for patients over 70 years, the cure was not reached (Fig. 2a and i). Overall, starting at age 30, increasing age was negatively associated with the probability of cure, probably due to the increased excess hazard of NPC related mortality (Supplementary Figure S3).

For patients with EBV DNA copies <2000, 2000–20,000, and >20,000 copies/mL, the likelihood of attaining the same life expectancy as that of the general population, regardless of tumor progression, were 78.3%, 77.6%, and 73.1%, respectively (Table 2). The corresponding probabilities of attaining the same life expectancy without tumor progression as that of the general population for the three categories were 73.5%, 71.8%, and 63.9%, respectively.
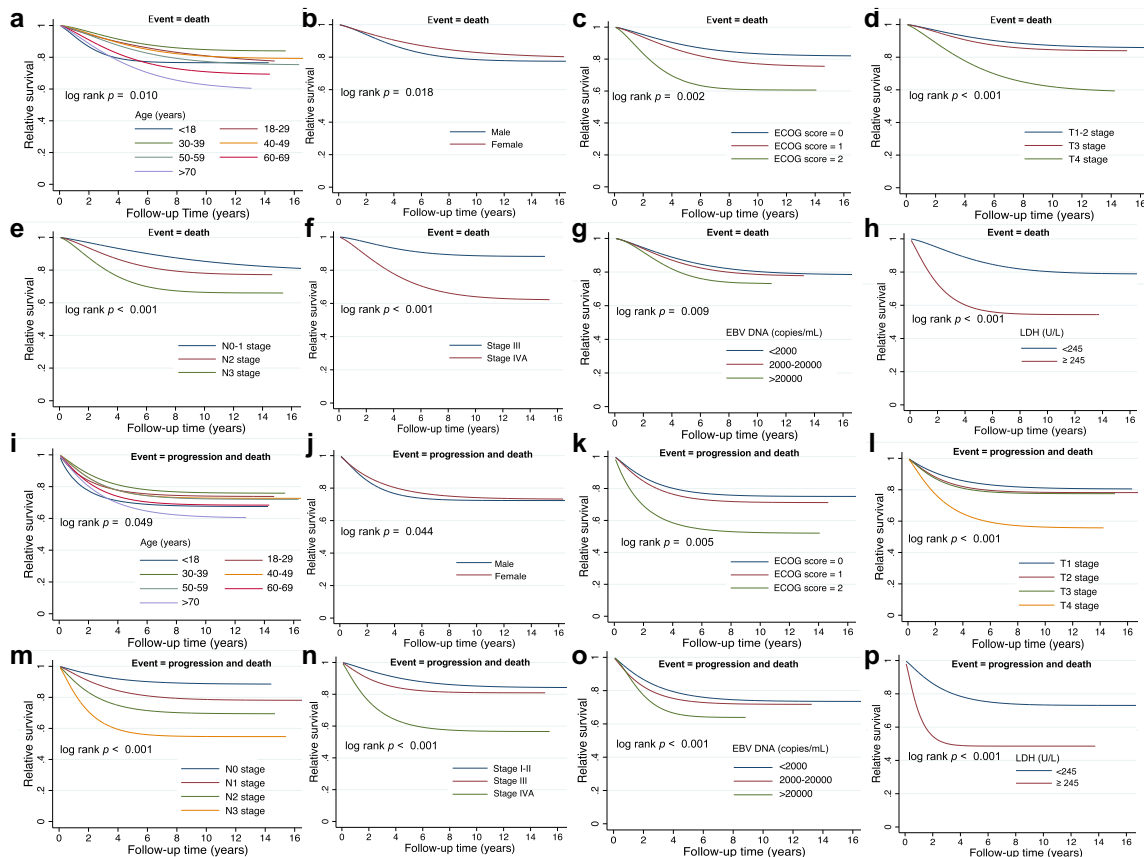
Fig. 2: Predicted relative survival (RS) curves by prognostic factors. With death as the uncured event, RS was calculated using the mixture model by (a) age, (b) sex, (c) ECOG score, (d) T stage, (e) N stage, (f) clinical stage, (g) EBV DNA load, and (h) LDH. With progression as the uncured event, RS was calculated using the nonmixture model by (i) age, (j) sex, (k) ECOG score, (l) T stage, (m) N stage, (n) clinical stage, (o) EBV DNA load, and (p) LDH. EBV, Epstein Barr virus; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; RS, relative survival.

Survival and cure time for the uncured groups

With death or progression as the uncured event, the estimated RS among uncured patients remained unfavorable (Fig. 1a and b), with the median OS and PFS rates of merely 3.7 years (95% CI, 3.2–4.2 years) and 1.8 years (95% CI, 1.7–2.0 years), respectively. The excess hazard rate among the uncured group showed a sharp increase within 2 years and continued to increase over time (Fig. 1c and d).

With death as the uncured event, cure time was determined by the time at which 95% of the uncured individuals succumbed. The cure time for the uncured cohort was 8.9 years (95% CI: 7.4–10.7 years) post-treatment (Fig. 1c). Hence, beyond the 8.9-year mark, the excess mortality associated with NPC was statistically insignificant, with the mortality rates of patients with NPC approaching those of the general population. With progression as the uncured event, cure time was determined by the time at which 95% of the uncured individuals had tumor progression. The cure time for

the uncured patients was 6.8 years (95% CI: 5.9–7.7 years) post-treatment (Fig. 1d). Supplementary Figure S4 shows that the cure times were attained within 10 years by most risk-stratified subgroups either with death or progression as the uncured event.

Sensitivity analysis

We investigated time points when OS and PFS rates could serve as reliable proxies for the cure fraction by using linear regression by calculating cure fractions and corresponding multipoint survival rates for each subgroup (Supplementary Table S1). An analysis with earlier time points for OS and PFS suggested that survival correlated well with cure fractions after 2 years ($R^2 = 0.77$ for OS and 0.84 for PFS; Fig. 3a and e). Stronger associations were noted between the OS and PFS rates at 5 years and the estimated cure fractions with excellent squared correlations ($R^2 = 0.92$ and 0.91; Fig. 3c and g). Moreover, linear regression showed excellent correlations between the 7-year OS and PFS

Characteristics	Number of patients (%)	Cure fraction (Event = death, 95% CI)	P value	Cure fraction (Event = progression and death, 95% CI)	P value
Sex			0.058		0.186
Male	4685 (74.2)	77.4 (74.4–80.2)		72.4 (70.4–74.3)	
Female	1630 (25.8)	79.4 (71.0–85.8)		73.1 (69.2–76.8)	
Age (years)			0.001		0.010
<18	130 (2.1)	76.6 (66.6–84.2)		67.5 (57.6–76.0)	
18–29	385 (6.1)	74.4 (50.1–89.4)		73.8 (68.1–78.8)	
30–39	1149 (18.2)	83.9 (79.0–87.9)		75.9 (72.0–79.3)	
40–49	1973 (31.2)	79.1 (73.8–83.7)		72.6 (69.5–75.5)	
50–59	1652 (26.2)	75.1 (67.7–81.4)		72.0 (68.0–75.6)	
60–69	816 (12.9)	69.0 (58.4–78.0)		68.3 (62.0–74.1)	
>70	210 (3.3)	59.2 (33.0–81.0)		60.2 (42.8–75.4)	
ECOG score			0.001		0.001
0	2510 (39.7)	81.9 (77.5–85.6)		75.0 (72.4–77.5)	
1	3698 (58.6)	75.2 (71.0–79.0)		71.2 (68.7–73.5)	
2	107 (1.7)	60.6 (47.5–72.4)		52.0 (39.5–64.3)	
Histological type			0.758		0.220
Nonkeratinizing	6127 (97.0)	78.2 (75.4–80.8)		72.5 (70.7–74.2)	
Keratinizing	188 (3.0)	73.1 (50.2–88.0)		68.1 (59.7–75.4)	
AJCC 8th T stage			<0.001		<0.001
T1	816 (12.9)	87.6 (80.5–92.3)		80.5 (75.2–84.9)	
T2	1017 (16.1)	83.8 (74.3–90.2)		78.2 (74.2–81.7)	
T3	2885 (45.7)	83.9 (80.3–87.0)		77.5 (75.1–79.8)	
T4	1597 (25.3)	58.6 (51.7–65.2)		55.7 (51.7–59.5)	
AJCC 8th N stage			<0.001		<0.001
N0	744 (11.8)	non-applicable		88.5 (81.2–93.2)	
N1	2189 (34.7)	non-applicable		78.1 (74.5–81.3)	
N2	2404 (38.1)	77.1 (73.3–80.5)		69.4 (66.6–72.1)	
N3	978 (15.4)	66.0 (60.7–70.8)		54.7 (50.6–58.8)	
AJCC 8th clinical stage			<0.001		<0.001
I–II	911 (14.4)	non-applicable			
III	3045 (48.2)	88.3 (85.2–90.8)		80.9 (78.6–83.0)	
IVA	2359 (37.4)	62.1 (57.3–66.6)		56.6 (53.5–59.5)	
EBV DNA (copies/mL)			0.008		<0.001
<2000	4824 (76.4)	78.3 (75.0–81.3)		73.5 (71.5–75.5)	
2000–20,000	942 (14.9)	77.6 (67.4–85.4)		71.8 (67.0–76.1)	
>20,000	549 (8.7)	73.1 (62.5–81.5)		63.9 (58.4–69.1)	
LDH (U/L)			<0.001		<0.001
<245	6123 (97.0)	78.8 (75.9–81.5)		73.0 (71.2–74.8)	
≥245	192 (3.0)	54.4 (45.1–63.4)		48.6 (40.0–57.2)	

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; EBV, Epstein–Barr virus; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NPC, nasopharyngeal carcinoma; OS, overall survival; PFS, progression-free survival.

Table 2: Univariate analysis of the cure fraction by risk characteristics of NPC.

rates and cure fractions (R^2 = 0.92 and 0.92; Fig. 3d and h).

Discussion

Patients were more interested in being informed whether and when they can be considered cured from NPC rather than simply being provided survival rates. This large-scale comprehensive study determined that despite significant heterogeneity in NPC, the concept of cure remained valid and reliable regardless of pretreatment characteristics. In the context of applying current treatment modalities, the cure was achieved across most risk-stratified subgroups of patients with NPC. With death and progression as uncured events, the probability of cure for patients with NPC was 78.1% and 74.1%, respectively. Cure probability was correlated with clinical risk factors, including age, ECOG score, TNM staging, EBV DNA copies, and LDH. For individual patients, the survival time with a 95% probability of cure was 7.1 and 4.7 years with death and progression as uncured events, respectively. These outcomes could help enhance clinical management, patient consultations, and clinical trials designs related to NPC.

To the best of our knowledge, this study is the first to utilize the cure model to quantitatively evaluate the probability of cure in patients with NPC receiving modern treatment modalities. Traditional survival analyses presume a constant risk of disease-associated mortality across all patients. In contrast, cure models more clearly reveal the heterogeneity of patients by stratifying them into cured and uncured groups.[28] In oncology research, cure models offer an intriguing path for investigating patient outcomes, because they facilitate the determination of whether and when individuals may be deemed cured of cancer.[10,13,29] Currently, there are few large-scale patient-based studies of NPC, which incorporate patients treated in modern clinical settings. Additionally, the survival rates reported in most current studies fail to consider the expected survival rates in the general population.[4,30] In comparison to previous studies, the current study's strengths lie in the large sample size of patients from four representative tertiary high-volume centers, including endemic and non-endemic areas of NPC in North, Central, Southwest, and South China. Furthermore, the detailed systematic collection of high-quality data with a long follow-up period provides a comprehensive and reliable picture of the survival trends in patients with NPC. Compared with clinical trials with strict inclusion criteria, the data obtained in this study are more likely to provide real-world prognostic estimates that are applicable to the general nonselected patients with NPC experiencing typical patterns of care. Another hallmark of this study was using RS data incorporating population survival and background mortality rather than relying on documentation of the precise cause of death, making it suitable for assessing long-term survival trends.

Using a different survival distribution for the uncured may lead to different results. To fit the mixture and nonmixture models, we chose the widely used Weibull distribution, which often provides a good fit.[18,19] Despite the high heterogeneity of NPC, the RS curves achieved plateaus. Additionally, the cure model
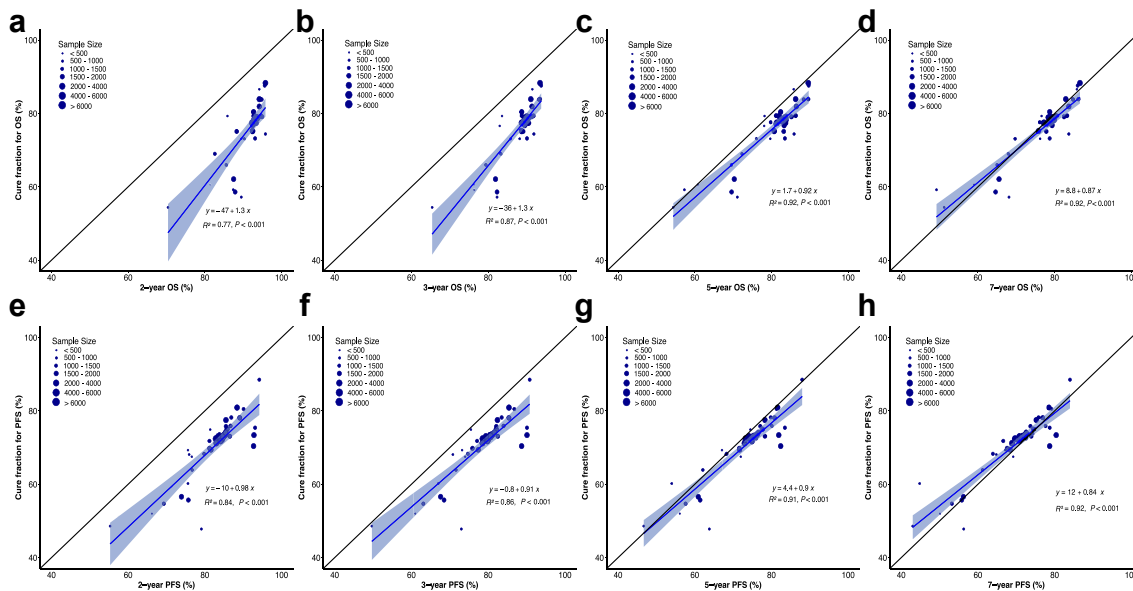
Fig. 3: Sensitivity analysis. The associations between (a) 2-, (b) 3-, (c) 5-, (d) 7-year OS, and (e) 2-, (f) 3-, (g) 5-, and (h) 7-year PFS rates and cure fractions were investigated using linear regression by calculating multipoint survival rates and cure fractions for each subgroup. Strong associations were noted between the OS and PFS rates from 5 years and the estimated cure fraction with excellent squared correlations (R^2). PFS, progression-free survival; OS, overall survival.

demonstrated convergence and exhibited a favorable fit in the majority of risk-stratified subgroups. Thus, the notion of the cure is statistically reasonable and robust for NPC. In addition, our analysis revealed that the likelihood of patients with NPC attaining the same life expectancy as non-NPC individuals in the general population reached 78.1%. Considering progression as the event, the likelihood of patients with NPC attaining the same probability of being alive and free from tumor progression as the general population was 72.4%. These data demonstrated the high probability of a possible cure after NPC treatment and contributed to a better estimation of the chances of a cure, thus helping doctors and patients to understand the long-term benefits of current treatments.

When does the long-term survivorship translate into a cure from NPC? Considering the favorable treatment outcome of NPC, this time depends largely on the survival time of long-term survivors/progression-free patients. At the individual level, cure probability is conditional and rises with the passing of survival time. For example, a patient surviving at 2 years post-treatment, a timeframe prone to most recurrences, has an 82% probability of being alive and tumor-free. To achieve a 95% certainty of long-term cure, the patient should wait approximately 4.7 years. Our findings were consistent with those of previous findings, indicating that despite the aggressive progression observed in patients with NPC during the initial years, later relapses beyond 5 years are rare.[6,7] These findings delineate a

pivotal landmark time point for patients, clinicians, and statisticians. For patients, attaining the landmark time point can provide reassurance and reduce anxiety levels that their excess hazard rates are likely to approximate that of the general population. From the clinicians' perspective, reaching this landmark milestone may justify a reduction in the frequency of cancer-specific monitoring and provide an economic surveillance strategy. Statisticians engaged in a prospective trial design may encounter limited applicability defining a late relapse as endpoints beyond the landmark time point. Instead, emphasis should be placed on variables such as quality of life, second primary cancer, and long-term psychosocial effects of cancer and treatment during subsequent follow-up.

When patients are considered cured is another important question during follow-up. Cure time is defined as the time the overall excess hazard rate reaches zero, which is determined by the uncured patients. With death and progression as the uncured events, the cure times were approximately 8.9 years and 6.8 years, respectively. Not surprisingly, cure time represents a more conservative approach to cure estimation and longer than the required survival time with a 95% probability of cure, probably because it emphasizes the uncured patient, particularly those with late recurrence/death. It is important to stress that cure time estimates are within 10 years by most risk-stratified subgroups, either with death or progression as the event. These results suggest that patients who remain alive and free

from progression beyond these time intervals may be deemed statistically cured with 95% certainty. Considering the low risks of progression/death beyond 10 years,[6] discontinuation of the systemic surveillance may be reasonable for patients with favorable prognoses.

Interestingly, we found that the actual observed survival rates at 5 years were close to the predicted cure fractions by a 45° line, indicating a good correlation between the predicted cure fraction and the actual observed survival rate. These findings indicated that survival at 5 years may exquisitely capture the ultimate cure fraction of the patient. The result supported the aforementioned conclusion that approximately 5 years are required to attain a 95% certainty of long-term cure without tumor progression. These results may provide oncologists and patients with a clearer insight into the probability of treatment success, thereby facilitating the development of appropriate surveillance and counseling strategies.

This study has some limitations. First, this study aimed to characterize the real-world survival estimations for patients receiving various therapeutic regimens. Thus, despite the large size of the enrolled cohort, sample sizes were limited in certain subgroups, such as patients treated with IC + IMRT. Second, the results of the study were derived from the Chinese patients, which limited its generalizability outside of China. However, it is well-known that the pathology proportion of NPC differ considerably between China and other regions, such as Europe or North America (different proportions of nonkeratinizing and keratinizing components). To justify this skewing, we estimated the cure fractions based on pathological type. Nevertheless, additional studies are still needed to investigate the cure probability in patients outside China to strengthen the external validity of the research.

In conclusion, our results underscored the validity of being statistically cured of NPC and shed light on the various possibilities for cure in the contemporary therapeutic context. The estimation in this study includes the probability that the life expectancy of patients with NPC will be at par with the general population and the probability of having the same life expectancy without progression compared with the general population. The probability of being cured rises with the extension of survival time. The clinical significance of the findings presented herein is to make informed post-treatment decisions and to provide patients with an accurate likelihood of treatment success.

Contributors

Yang Liu, Xin Liu, Shiran Sun, Shanshan Guo, Jingbo Wang, and Junlin Yi contributed to conception and design of the study. Yexiong Li, Junlin Yi, and Jingbo Wang contributed to administrative support. Yaqian Han, Mei Feng, Jianghu Zhang, Yang Liu, Xiaodong Huang, Kai Wang, Yuan Qu, Xuesong Chen, Runye Wu, Ye Zhang, Jingwei Luo, Junlin Yi, Jingbo Wang, and Chaosu Hu contribute to provision of study materials or patients. Yang Liu, Runye Wu, Yexiong Li, Junlin Yi, and Jingbo Wang contribute to collection and assembly of data. Yang Liu, Xiaodong Huang, Kai Wang, Yuan Qu, Xuesong Chen, Ye Zhang, Jianghu Zhang, Jingwei Luo, Junlin Yi, and Jingbo Wang contribute to data analysis and interpretation. All the authors contribute to manuscript writing. All the authors contribute to final approval of manuscript. Shanshan Guo, Jingbo Wang and Junlin Yi had verified the underlying data and had direct access to raw data. Shanshan Guo, Jingbo Wang and Junlin Yi had final responsibility for the decision to submit for publication.

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