

Subdivision of metachronous metastatic nasopharyngeal carcinoma based on the framework of TNM-9: A recursive partitioning analysis of real-world data

Daqiang Huang

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Hanchuan Xu

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Xiaoya Xie

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Yiyun Huang

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Kexin Lin

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Yuan Huang

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Lili Zhu

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Yahan Zheng

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Chaobin Huang

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Youping Xiao

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Jianji Pan

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Shaojun Lin

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Junxin Wu

Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital

Qiaojuan Guo

guoqiaojuan@163.com

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Abstract

Purpose: To validate the prognostic value of the M1 category in version nine of the AJCC/UICC TNM staging system (TNM-9) in metachronous metastatic nasopharyngeal carcinoma (mmNPC) and to develop a refined M1 classification for improved risk stratification.

Methods: Patients with newly diagnosed mmNPC (2015–2024) were analyzed and restaged per TNM-9 M1 criteria. Independent prognostic factors from multivariate Cox analysis were integrated using recursive partitioning analysis (RPA) to establish an RPA-based M1 classification (RPA-M1). Model performance was assessed using Harrell's C-index, time-dependent AUC, and Akaike information criterion (AIC).

Results: Among 218 patients, 111 (50.9%) were M1a and 107 (49.1%) M1b. The M1a subgroup demonstrated significantly higher 3-year overall survival (OS) than the M1b subgroup (63.2% vs. 40.8%, $P < 0.001$). Both the TNM-9 M1 category and disease-free interval (DFI) were independent prognostic factors for OS (both $P < 0.05$). The RPA model stratified patients into distinct prognostic groups: RPA-M1a (≤ 3 metastatic lesions and DFI > 12 months) and RPA-M1b (> 3 lesions or DFI ≤ 12 months), with 3-year OS rates of 74.6% and 40.6%, respectively ($P < 0.001$). The RPA-M1 classification showed superior prognostic discrimination compared with the TNM-9 M1 stage, evidenced by higher C-index, time-dependent AUCs, and lower AIC. Metastasis-directed therapy improved OS only in the RPA-M1a subgroup, while intensified systemic therapy primarily benefited the RPA-M1b subgroup.

Conclusion: The TNM-9 M1 category is applicable to mmNPC. The novel RPA-M1 classification, which integrates metastatic burden and DFI, offers superior risk stratification and enables more precise prognostication and individualized management.

Introduction

Distant metastasis remains the predominant pattern of treatment failure in nasopharyngeal carcinoma (NPC), occurring as metachronous metastasis (mmNPC) in approximately 15%-30% of patients after curative-intent radical chemoradiotherapy.(1, 2) Like de novo metastatic NPC (M1-NPC),(3, 4) mmNPC represents a distinct clinical entity with highly heterogeneous outcomes,(5–7) underscoring the urgent need for effective risk stratification to guide personalized management.

The recent introduction of the ninth edition of the AJCC/UICC TNM staging system (TNM-9) marks a significant advancement by incorporating, for the first time, a subdivision of the M1 category for NPC into M1a (≤ 3 metastatic lesions) and M1b (> 3 lesions).(3) This classification has demonstrated robust prognostic value in patients with newly diagnosed M1-NPC. However, a pivotal and unresolved question is whether this M1 stratification, derived from de novo metastatic disease, can be effectively applied to prognosticate and guide treatment in patients with mmNPC.

Prior to TNM-9, several studies(5–7) attempted to subclassify mmNPC and identified prognostic factors including metastatic lesion count, specific organ involvement, EBV-DNA copy number, and disease-free interval (DFI)—the time from initial diagnosis to metastasis detection. However, these classification systems were limited by substantial heterogeneity in patient selection, particularly with regard to treatment intensity—not all enrolled patients receiving standardized systemic chemotherapy.(5, 6) Moreover, inter-laboratory variability in EBV-DNA detection poses a persistent challenge across many institutions,(8–10) complicating its generalizability and clinical translation.

To address these limitations, we conducted this study to validate the TNM-9 M1 category—a globally unified staging framework—in a consecutive cohort of mmNPC patients from our institution. We further evaluated additional prognostic factors, particularly DFI, to assess the need for refining M1 stratification specifically for mmNPC. By integrating these variables using recursive partitioning analysis (RPA), we aimed to develop an optimized M1 subclassification tailored to this distinct clinical entity, thereby enabling more precise risk stratification and individualized therapeutic decision-making.

Materials and Methods

Study Population

After obtaining institutional review board approval, we identified patients with newly diagnosed mmNPC treated at our institution between 2015 and 2024 as potential candidates. Inclusion criteria were: (1) age 18–70 years; (2) measurable metastatic lesions; (3) availability of complete baseline clinical and imaging data for efficacy assessment, with all cases restaged according to the TNM-9 classification; and (4) receipt of at least two cycles of palliative chemotherapy (PCT). The primary exclusion criteria were: (1) metastatic disease was identified within 6 months interval between diagnosis of metastatic disease and primary diagnosis; or (2) a history of other concurrent or prior malignancies.

Imaging Assessment for Restaging and Data Collection

All patients underwent comprehensive baseline imaging for metastatic restaging, including physical examination, fiberoptic nasopharyngoscopy, magnetic resonance imaging or computed tomography (CT) of the head and neck, chest CT, abdominal ultrasonography or CT, whole-body bone scan, hematologic profiling, and positron emission tomography/CT (PET/CT) when indicated. The number of metastases and involved organ sites were determined by centralized review of baseline imaging studies by specialized radiologists. For this analysis, the liver, lungs, bones, and distant lymph node basins (defined as those beyond the cervical region) were each considered distinct metastatic organs. Furthermore, within the category of lymph node involvement, each major lymphatic drainage area—such as the axillary, mediastinal, retroperitoneal, or inguinal regions—was counted as a single metastatic lesion.(4, 11, 12)

Treatment

All patients received at least two cycles of systemic therapy. The chemotherapeutic regimens included GP (gemcitabine and platinum), TP (docetaxel and platinum), PF (platinum and 5-fluorouracil), TPF (docetaxel, platinum, and 5-fluorouracil), and TPC (docetaxel, platinum, and capecitabine). The immune checkpoint inhibitors (ICIs) used included toripalimab, camrelizumab, sintilimab, tislelizumab, pembrolizumab, penpulimab, and nivolumab. These treatments were administered in 3-week cycles. Following 2018,(13–16) ICIs were increasingly adopted for mmNPC cases.

Based on physician assessment and patient preference, maintenance therapy (MT) consisted of ICIs, capecitabine/S-1, or a combination thereof. Select patients received metastasis-directed therapy (MDT)—including palliative radiotherapy, surgical resection, or ablation—to alleviate local symptoms and eradicate metastases in sites such as bone, liver, and lungs. MDT was applied either comprehensively to all metastatic sites or selectively to a subset.

Follow-up

Tumor response was assessed every two to three cycles during systematic treatment and every 3–6 months thereafter. Primary lesions were evaluated via head and neck MRI, while distant metastases were monitored via PET-CT, MRI, CT, or whole-body bone scans. The final follow-up date was March 2025. The primary endpoint was overall survival (OS), calculated from the mmNPC diagnosis to the last confirmed survival date or death. The secondary endpoint was progression-free survival (PFS), defined as the time from diagnosis of mmNPC to the first recorded disease progression or death. The disease-free interval (DFI) was defined as the interval between the onset of the primary treatment for non-metastatic NPC and the time of the first detection of distant metastasis. The following progression patterns—polymetastatic disease, repeat oligorecurrence, induced oligorecurrence, repeat oligoprogression, and repeat oligopersistence—were defined according to the EORTC/ESTRO consensus on oligometastatic disease established by Matthias et al.(17) Consistent with the TNM-9 framework, oligometastasis was defined as ≤ 3 lesions and polymetastasis as > 3 lesions.

Statistical Analysis

Continuous variables were described using medians and interquartile ranges (IQRs), analyzed and compared using the Mann–Whitney U or Kruskal–Wallis test. Categorical data were presented as frequencies with percentages and compared using the chi-square test or Fisher's exact test, as appropriate. The optimal cutoff value for DFI was determined and visualized using X-tile software (version 3.6.1; Yale University, New Haven, CT, USA). A 10-fold cross-validation was subsequently performed using R packages (survival, maxstat, and caret) to validate the stability of the identified cutoff. Survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate Cox proportional hazards models were used to identify independent prognostic factors. Recursive partitioning analysis (RPA) was performed using an online website

(<http://rpa.renlab.org>). Predictive performance was evaluated via AUC and Harrell's C-index. All analyses used SPSS 29.0.1.0 and R 3.6.3, with two-tailed P-value < 0.05 considered statistically significant.

Result

Patient Characteristics

Patient selection details are depicted in Figure S1. A total of 218 patients were included, comprising 173 males (79.4%) and 45 females (20.6%). Using X-tile software, 12 months was identified as the optimal DFI cutoff (Figure S2), which was subsequently confirmed by 10-fold cross-validation. According to this cutoff, 79 patients (36.2%) had a DFI $\leq$ 12 months and 139 (63.8%) had a DFI > 12 months. Detailed clinical characteristics are outlined in Table 1. According to the TNM-9 classification, 111 patients (50.9%) were categorized as M1a and 107 (49.1%) as M1b. Compared with the M1a group, the M1b group had a significantly higher proportion of multiple-organ metastases, concurrent with locoregional recurrence, bone involvement, and distant lymph node (LN) involvement. Both M1 subgroups received similar intensity of PCT and MT. Additionally, a higher proportion of M1a patients underwent MDT compared to M1b patients (67.5% vs. 27.1%, $P < 0.001$). Furthermore, among those receiving MDT, a higher proportion of M1a patients received treatment for all lesions compared to M1b patients (84.4% vs. 27.6%).

Table 1
Patient and treatment characteristics in the entire cohort and the M1a and M1b subgroups.

Characteristic	Entire cohort, n (%)	M1a, n (%)	M1b, n (%)	P value
	n = 218	n = 111 (50.9%)	n = 107 (49.1%)	
Age, median (IQR), y	48 (37,55)	46 (41,54)	49 (38,55)	0.961
Sex				0.716
Male	173 (79.4%)	87 (78.4%)	86 (80.4%)	
Female	45 (20.6%)	24 (21.6%)	21 (19.6%)	
No. of metastatic organs				< 0.001
Single organ	130 (59.6%)	92 (82.9%)	38 (35.5%)	
Multiple organs (≥ 2)	88 (40.4%)	19 (17.1%)	69 (64.5%)	
Locoregional recurrence				0.047
No	184 (84.4%)	99 (89.2%)	85 (79.4%)	
Yes	34 (15.6%)	12 (10.8%)	22 (20.6%)	
Bone involvement				0.002
No	133 (61%)	79 (71.2%)	54 (50.5%)	
Yes	85 (39%)	32 (28.8%)	53 (49.5%)	
Liver involvement				0.292
No	146 (67%)	78 (70.3%)	68 (63.6%)	
Yes	72 (33%)	33 (29.7%)	39 (36.4%)	
Lung involvement				0.142
No	123 (56.4%)	68 (61.3%)	55 (51.4%)	
Yes	95 (43.6%)	43 (38.7%)	52 (58.6%)	
Distant LN involvement				< 0.001
No	154 (70.6%)	92 (82.9%)	62 (57.9%)	
Yes	64 (29.4%)	19 (17.1%)	45 (42.1%)	
PCT				0.777
< 4 cycles	114 (52.3%)	57 (51.4%)	57 (53.3%)	

Characteristic	Entire cohort, n (%)	M1a, n (%)	M1b, n (%)	P value
	n = 218	n = 111 (50.9%)	n = 107 (49.1%)	
≥ 4 cycles	104 (47.7%)	54 (48.6%)	50 (46.7%)	
MDT				< 0.001
No	125 (57.3%)	47 (42.3%)	78 (72.9%)	
Yes	93 (42.7%)	64 (67.5%)	29 (27.1%)	
MT				0.253
No	73 (33.5%)	33 (29.7%)	40 (37.4%)	
Yes	145 (66.5%)	77 (70.3%)	67 (62.6%)	
DFI (months)				0.141
≤ 12	79 (36.2%)	45 (31.5%)	44 (41.1%)	
> 12	139 (63.8%)	76 (68.5%)	63 (58.9%)	

Oncological outcomes

Of 166 patients who experienced disease progression, 121 died from disease, including two fatalities from treatment-related complications. Progression patterns at metastatic sites were evaluable in 119 patients and categorized as follows (Table S1): polymetastatic disease (72, 60.5%), repeat oligorecurrence (38, 31.9%), induced oligorecurrence (6, 5.0%), repeat oligoprogression (2, 1.7%), and repeat oligopersistence (1, 0.9%).

With a median follow-up of 32 months (IQR: 19–59), the median PFS (mPFS) and OS (mOS) for the entire cohort were 16 and 42 months, respectively. The corresponding 3-year PFS and OS rates were 31.6% and 52.1%. The M1a subgroup revealed a significantly better OS (mOS: not reached vs. 29 months; 3-year OS: 63.2% vs. 40.8%, $P < 0.001$, Fig. 1B) and PFS (mPFS: 35 vs. 11 months; 3-year PFS: 49.2% vs. 13.9%, $P < 0.001$, Fig. 1E) than the M1b subgroup. A prolonged DFI (> 12 months) was also associated with significantly improved OS (mOS: 59 vs. 24 months; 3-year OS: 58.1% vs. 41.7%, $P = 0.005$, Fig. 1C) and PFS compared to a shorter DFI (≤ 12 months) (mPFS: 24 vs. 8 months; 3-year PFS: 37.2% vs. 21.5%, $P < 0.001$, Fig. 1F). Corresponding univariate analysis results are presented in Table 2 and Table S2. Multivariate analysis (MVA), adjusted for age, sex, and specific organ involvement, identified both the TNM-9 M1 category (HR, 1.831; 95% CI, 1.178–2.845; $P = 0.007$) and DFI (HR, 1.635; 95% CI, 1.121–2.384; $P = 0.011$) as independent adverse prognostic factors for OS (Table 2). Consistent results were observed for PFS (both $P < 0.05$; Table S2).

Table 2
Univariate and multivariate Cox regression analysis of OS in the whole cohort.

Characteristics	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age, median (IQR), y	1.014 (0.997–1.031)	0.101	1.018 (1.002–1.035)	0.031
Sex				
Female	Reference		Reference	
Male	1.581 (0.969–2.582)	0.067	1.477 (0.891–2.449)	0.130
No. of metastatic organs				
Single organ	Reference		Reference	
Multiple organs (≥ 2)	1.533 (1.072–2.191)	0.019	1.226 (0.607–2.477)	0.571
Locoregional recurrence				
No	Reference		Reference	
Yes	1.443 (0.908–2.295)	0.121	1.139 (0.588–1.959)	0.596
M1 category in TNM-9				
M1a	Reference		Reference	
M1b	2.148 (1.486–3.105)	< 0.001	1.831 (1.178–2.845)	0.007
Bone involvement				
No	Reference		Reference	
Yes	1.393 (0.971–1.999)	0.072	1.073 (0.588–1.959)	0.819
Liver involvement				
No	Reference		Reference	
Yes	1.371 (0.949–1.979)	0.093	1.058 (0.567–1.976)	0.860
Lung involvement				
No	Reference		Reference	
Yes	0.867 (0.604–1.244)	0.439	0.897 (0.468–1.719)	0.744
Distant LN involvement				
No	Reference		Reference	
Yes	1.128 (0.768–1.657)	0.538	0.894 (0.497–1.609)	0.708

Characteristics	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
DFI (months)				
≤ 12	Reference		Reference	
> 12	1.668 (1.164–2.390)	0.005	1.635 (1.121–2.384)	0.011

Proposal for future refinement of the M1 category in TNM-9 for mmNPC

Using the RPA algorithm (Fig. 1A), we stratified the cohort into two distinctly prognostic subgroups: RPA-M1a (n = 76; ≤ 3 metastatic lesions and DFI > 12 months); and RPA-M1b (n = 142; > 3 lesions or DFI ≤ 12 months), which exhibited markedly distinct OS (mOS: not reached vs. 29 months; 3-year OS: 74.6% vs. 40.6%, $P < 0.001$) and PFS (mPFS: 45 vs. 10 months; 3-year PFS: 56.0% vs. 19.0%, $P < 0.001$) (Fig. 1D, G). The Cox regression model, adjusting for age, sex, and specific organ involvement, confirmed that higher RPA groupings conferred a higher risk of death and disease progression (Table 3 and S3).

Table 3
Multivariate Cox regression analysis of OS in the PRA-M1 cohort.

Characteristics	Hazard ratio (95% CI)	P value
Age, median (IQR), y	1.015 (0.999–1.032)	0.064
Sex		
Female	Reference	
Male	1.465 (0.886–2.423)	0.137
No. of metastatic organs		
Single organ	Reference	
Multiple organs (≥ 2)	1.257 (0.630–2.508)	0.516
Locoregional recurrence		
No	Reference	
Yes	1.106 (0.681–1.797)	0.638
PRA-M1 subgroups		
RPA-M1a	Reference	
PRA-M1b	2.862 (1.768–4.632)	< 0.001
Bone involvement		
No	Reference	
Yes	1.051 (0.573–1.927)	0.873
Liver involvement		
No	Reference	
Yes	1.001 (0.541–1.854)	0.997
Lung involvement		
No	Reference	
Yes	0.850 (0.442–1.634)	0.626
Distant LN involvement		
No	Reference	
Yes	0.876 (0.482–1.595)	0.666

The RPA model demonstrated superior prognostic discrimination for OS compared to the TNM-9 M1 stage. This was evidenced by a higher C-index (0.657 vs. 0.635), higher time-dependent AUC values (1-

year: 0.660 vs. 0.635; 3-year: 0.708 vs. 0.672), and a lower AIC (1175.1 vs. 1186.7) (Table S4).

Efficacy of PCT, MDT and MT in the RPA-M1 subdivisions

Baseline characteristics of the RPA-M1 subgroups are detailed in Tables S5 and S6. In the entire cohort, receipt of PCT (≥ 4 cycles), MDT, or MT was associated with significantly improved OS and PFS compared to non-receipt (all $P < 0.05$, Fig. 2A-C and S3A-C). MVA confirmed PCT and MT as independent prognostic factors for OS (both $P < 0.05$), whereas MDT showed only a trend ($P = 0.074$; Table 4). All three modalities were independent prognostic factors for PFS (Table S7). In the favorable RPA-M1a subgroup, MDT significantly improved both OS (mOS: not reached vs. 63 months; 3-year OS: 85% vs. 60%, $P = 0.005$; Fig. 2E) and PFS ($P = 0.027$; Figure S3E). Notably, more intensive PCT failed to demonstrate significant improvements in either OS or PFS (all $P > 0.05$; Figs. 2D and S3D). These findings were further validated after adjustment for potential confounders in MVA as detailed in Tables 4 and S7. MT was associated with a significant OS benefit in univariate analysis (mOS: not reached vs. 48 months; 3-year OS: 81.4% vs. 59.5%, $P = 0.007$; Fig. 2F). However, after adjusting for confounders in MVA, this effect was attenuated to a non-significant trend ($P = 0.057$; Tables 4). Although MT yielded numerically higher PFS rates (mPFS: 49 vs. 29 months; 3-year PFS: 60.0% vs. 47.4%), this difference did not reach statistical significance in univariate analysis ($P = 0.147$; Figure S3F), and MVA confirmed the absence of a significant independent effect on PFS ($P > 0.05$; Table S7). Notably, despite these negative findings for conventional survival endpoints, MT did significantly prolong polymetastatic-free survival (median: not reached vs. 42 months; 3-year: 79.6% vs. 65.9%, $P < 0.05$; Figure S4), underscoring its potential clinical value in delaying extensive metastatic dissemination beyond what is captured by standard PFS assessment.

Table 4
Multivariate analysis of OS in the whole cohort and each RPA-M1 subgroups.

Characteristics	Whole cohort		RPA-M1a cohort		RPA-M1b cohort	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age, median (IQR), y	1.011 (0.994–1.028)	0.204	0.998 (0.948–1.049)	0.925	1.010 (0.992–1.028)	0.293
Sex						
Female	Reference		Reference		Reference	
Male	1.491 (0.903–2.465)	0.119	1.980 (0.428–9.160)	0.382	1.305 (0.760–2.240)	0.335
No. of metastatic organs						
Single organ	Reference		Reference		Reference	
Multiple organs (≥ 2)	1.232 (0.606–2.505)	0.564	1.647 (0.243–11.151)	0.609	1.337 (0.610–2.933)	0.469
Locoregional recurrence						
No	Reference		Reference		Reference	
Yes	1.128 (0.680–1.872)	0.641	1.439 (0.314–6.593)	0.639	1.106 (0.613–1.995)	0.737
Bone involvement						
No	Reference		Reference		Reference	
Yes	1.220 (0.666–2.236)	0.519	0.574 (0.090–3.676)	0.558	1.219 (0.621–2.3939)	0.565
Liver involvement						
No	Reference		Reference		Reference	
Yes	1.058 (0.557–2.009)	0.866	0.380 (0.039–3.666)	0.403	1.186 (0.583–2.413)	0.637

Characteristics	Whole cohort		RPA-M1a cohort		RPA-M1b cohort	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Lung involvement						
No	Reference		Reference		Reference	
Yes	0.738 (0.383–1.423)	0.364	0.273 (0.027–2.797)	0.274	0.831 (0.399–1.734)	0.622
Distant LN involvement						
No	Reference		Reference		Reference	
Yes	0.932 (0.502–1.733)	0.825	0.660 (0.061–7.104)	0.731	0.884 (0.450–1.734)	0.719

PCT						
< 4 cycles	Reference		Reference		Reference	
≥ 4 cycles	0.589 (0.398– 0.871)	0.008	0.527 (0.202– 1.374)	0.190	0.526 (0.334– 0.828)	0.005
MDT						
No	Reference		Reference		Reference	
Yes	0.667 (0.428– 1.040)	0.074	0.252 (0.093– 0.685)	0.007	0.893 (0.533– 1.498)	0.699
MT						
No	Reference		Reference		Reference	
Yes	0.382 (0.261– 0.559)	< 0.001	0.368 (0.131– 1.030)	0.057	0.388 (0.249– 0.604)	< 0.001
RPA-M1 subgroups						
RPA-M1a	Reference		-	-	-	-
RPA-M1b	2.385 (1.437– 3.958)	< 0.001	-	-	-	-
<i>Abbreviations:</i> CI, confidence interval; LN, lymph node; MDT, metastasis-directed therapy; MT, maintenance therapy; OS, overall survival; PCT, palliative chemotherapy; RPA, recursive-partitioning analysis.						

In the higher-risk RPA-M1b subgroup, both PCT (≥ 4 cycles) and MT were associated with significantly improved outcomes. Patients receiving ≥ 4 PCT cycles had superior OS (mOS: 36 vs. 24 months; 3-year OS: 49.5% vs. 34.6%, $P = 0.011$; Fig. 2G) and a trend toward better PFS (mPFS: 14 vs. 9 months; 3-year PFS: 19.7% vs. 18.6%, $P = 0.081$; Figure S3G). Similarly, MT was associated with superior OS (mOS: 38 vs. 18 months; 3-year OS: 51.2% vs. 21.1%, $P < 0.001$; Fig. 2I) and PFS (mPFS: 13 vs. 8 months; 3-year PFS: 25.1% vs. 8%, $P < 0.001$; Figure S3I). In contrast, MDT conferred no significant benefit in either OS or PFS in this subgroup (both $P > 0.05$; Figs. 2H and S3H). These prognostic findings were further validated after adjustment for potential confounders as detailed in Table 4 and S7.

Discussion

To our knowledge, both mmNPC(5–7) and M1-NPC(4) are highly heterogeneous diseases with considerable prognostic variability. Although TNM-9 subdivides M1-NPC into distinct categories, its applicability to mmNPC has remained uncertain. This study yielded several important findings. First, we demonstrated that the TNM-9 M1 category is applicable to mmNPC and that both this category and DFI

independently predict prognosis. By integrating these factors via RPA, we developed a refined two-tier system: RPA-M1a (≤ 3 metastases and DFI > 12 months) and RPA-M1b (> 3 metastases or DFI ≤ 12 months). This RPA-M1 system demonstrated robust discriminatory power, with 3-year OS rates of 74.6% versus 40.6% (mOS: not reached versus 29 months, $P < 0.001$). Moreover, it effectively stratified therapeutic benefit: MDT improved outcomes exclusively in the RPA-M1a subgroup, whereas intensified systemic therapy only improved outcomes in the RPA-M1b subgroup. This study represents the first validation of the prognostic utility of the TNM-9 M1 category in mmNPC and introduces an enhanced risk stratification model that integrates both metastatic burden and DFI.

Prior to TNM-9,(3) several subclassification systems were proposed for mmNPC.(5–7) The earliest and largest study to date, conducted by Shen et al. from Sun Yat-sen University Cancer Center (SYSUCC),(5) analyzed a multicenter cohort of 1,172 mmNPC patients and proposed a three-tiered system based on anatomic features: M1a (single lesion in a single organ), M1b (multiple lesions in a single organ), and M1c (metastases in multiple organs). With 86.3% of patients receiving PCT, median OS was 25.6 months. Another SYSUCC study(6) by Zheng et al. ($n = 817$) stratified patients into four prognostic groups as follows: M1a (low EBV DNA + oligo lesion ≤ 2), M1b (low EBV DNA + multiple lesions > 2), M1c (high EBV DNA + no liver involvement), and M1d (high EBV DNA + liver involvement). With 65% of patients receiving chemotherapy, they reported a mOS of 17.7 months, with 1- and 3-year OS rates of 75.9% and 30.5%, respectively. In both studies, DFI was not identified as a significant prognostic factor.

Despite this, the prognostic value of DFI has been demonstrated in three SYSUCC studies(18–20) focusing on liver-only(19) or bone-only(20) metastases, and a subsequent analysis from Fujian encompassing the full mmNPC spectrum.(21) In 2022, Peng et al. from Jiangsu(7) developed a prognostic nomogram for mmNPC that incorporated DFI alongside metastatic burden and other clinical variables. The 1- and 3-year OS rates were 76.1% and 39.8%, respectively. Consistent with Peng et al's study, the current series demonstrated that DFI retains independent prognostic significance beyond TNM-9 M1 category. The inconsistency in the prognostic value of DFI across studies likely reflects differences in study populations, particularly regarding inclusion criteria and treatment intensity. Both the study by Peng et al.(7) and our cohort had uniformly high rates of chemotherapy exposure—all patients in Peng's study received at least one cycle of chemotherapy, while 100% of patients in our cohort received chemotherapy of at least two cycles and 23.9% of them received ICI during PCT phase. Our cohort demonstrated superior survival outcomes (mOS 42 months; 3-year OS 52.1%), suggesting that ensuring a minimum standard of treatment intensity is essential for elucidating the true prognostic impact of metastatic burden and temporal factors such as DFI.

Systemic therapy remains the cornerstone of treatment for metastatic NPC.(22–24) However, the integration of comprehensive strategies, including MDT(6, 7, 18–21, 25–28) and MT(14–16, 29, 30) has substantially improved outcomes in recent years. Consistent with previous reports,(7, 21) the present study confirmed that a higher number of PCT cycles (≥ 4) was associated with significantly improved OS in the overall cohort (HR, 0.589; 95% CI, 0.398–0.871, $P = 0.008$), corroborating findings from Zheng et al. (21) and Peng et al.(7) Notably, none of the aforementioned studies performed subgroup analyses to

explore whether the benefit of intensified PCT varied according to patient risk profiles. In the present study, subgroup analysis revealed that survival benefit of intensified PCT was confined to the RPA-M1b subgroup, with no significant benefit observed in the RPA-M1a subgroup. This finding suggests that for patients with low metastatic burden, enhancing PCT intensity may be unnecessary—particularly in the immunotherapy era, where the optimal PCT duration remains to be defined. Moreover, the potential contribution of MDT and maintenance therapy in this population may further diminish the incremental value of intensified PCT. Our findings underscore the need for well-designed prospective studies to determine the optimal intensity of palliative chemotherapy within the context of multimodality treatment.

Following three landmark prospective phase III immunotherapy trials(14–16) and two pivotal non-immunotherapy studies(29, 30) establishing capecitabine maintenance as a standard option, both immunotherapy and oral maintenance therapy have been widely adopted in real-world practice and are now recommended by treatment guidelines for metastatic NPC. However, whether all patients with metastatic NPC derive equivalent benefit from MT remains unclear, particularly given the limited data specifically addressing mmNPC. In the present study, MT was associated with improved survival in the overall cohort. Subgroup analysis further revealed that the survival benefit of MT was more pronounced in the RPA-M1b subgroup, whereas no significant benefit was observed in the RPA-M1a subgroup. This differential effect may be attributable to the confounding impact of effective prior PCT and MDT in the low-risk subgroup, potentially attenuating the incremental contribution of MT. These findings suggest that in the context of sufficiently intensive PCT and MDT, whether MT confers additional benefit—and the optimal regimen and duration thereof—warrants further investigation through well-designed prospective studies. Emerging evidence suggests that dynamic monitoring of EBV DNA may inform maintenance treatment strategies.(31, 32)

MDT is currently recommended as a treatment option for patients with oligometastatic disease by major clinical practice guidelines, including those of the National Comprehensive Cancer Network (NCCN). Multiple retrospective series have shown that MDT—such as surgery or radiotherapy directed at limited metastatic lesions—is associated with improved survival in selected low-risk mmNPC patients.(6, 7, 33) Patient selection in these studies has typically been guided by metastatic burden, EBV-DNA level, DFI, and nomogram-based risk models. Aligning with these findings, the present study demonstrated that MDT significantly improved outcomes in the RPA-M1a subgroup, further corroborating prior evidence from multiple centers. However, our analysis also revealed that the survival benefit of MDT was limited in the RPA-M1b subgroup, suggesting that for patients with polymetastatic disease, treatment strategies should prioritize more effective systemic therapy, such as the combination of antibody-drug conjugates (ADCs)(34) and ICIs(13–16), to achieve maximal tumor burden reduction. Notably, only 23.8% of patients in our cohort incorporated ICIs in the PCT phase.

Several limitations should be considered when interpreting our findings. First, the retrospective, single-center design may introduce selection bias and limit the generalizability of the results. Second, the moderate sample size constrains statistical power for certain subgroup analyses and precluded a detailed evaluation of therapy efficacy across specific metastatic sites. Third, reflecting the real-world

adoption curve of immunotherapy, only a subset of patients in this cohort received ICIs, which may affect the extrapolation of outcomes to the current treatment landscape. With the advent of more effective systemic regimens, including the integration of immune checkpoint inhibitors with chemotherapy for all patients, the net impact of MDT to metastatic lesions should be re-evaluated. Finally, our model did not incorporate plasma EBV DNA, a known prognostic biomarker in NPC. While this strategy enhances the model's practicality by avoiding inter-laboratory assay variability of EBV DNA detection,(8–10) future iterations could be strengthened by including standardized biomarker data.

Conclusion

This study validates the prognostic utility of the TNM-9 M1 subclassification in mmNPC and identifies DFI as an independent prognostic factor beyond anatomic metastatic burden. By integrating these two factors through RPA, we established a refined RPA-M1 classification that stratifies patients into two distinct prognostic subgroups: RPA-M1a (≤ 3 metastases and DFI > 12 months) and RPA-M1b (> 3 metastases or DFI ≤ 12 months). This novel system demonstrates superior prognostic discrimination compared to the TNM-9 M1 category alone and, importantly, informs treatment decision-making. Our findings provide a practical, staging-aligned framework that addresses a critical gap left by prior classification systems and recent prospective trials. Prospective studies are warranted to validate this risk-stratified approach and to further refine prognostic precision and individualized therapeutic strategies making.

Abbreviations

AIC

akaike information criterion

AUC

area under receiver operating characteristic curve

ADCs

antibody-drug conjugates

CI

confidence interval

C-index

harrell's concordance index

CT

computed tomography

DFI

disease-free interval

GP

gemcitabine and platinum

LN

lymph node

MDT
metastasis-directed therapy
MT
maintenance therapy
M1-NPC
de novo metastatic NPC
MVA
multivariate analysis
mmNPC
metachronous metastatic nasopharyngeal carcinoma
NCCN
national comprehensive cancer network
NPC
nasopharyngeal carcinoma
OS
overall survival
PFS
progression-free survival
PCT
palliative chemotherapy
PET/CT
positron emission tomography/CT
PF
platinum and 5-fluorouracil
RPA
recursive partitioning analysis
ICIs
immune checkpoint inhibitors
IQRs
interquartile ranges
TP
docetaxel and platinum
TPF
docetaxel,platinum and 5-fluorouracil
TPC
docetaxel,platinum and capecitabine

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Boards of Fujian Cancer Hospital. The study was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

Clinical trial number

Not applicable

Consent for publication

Not applicable

Competing interests

All the other authors declare that he/she has no conflict of interest.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

DH, HX and XX contributed equally to this work. DH, HX and SL conceived and designed the study. DH, HX, XX, YYH, KL, YH, LZ, YZ and CH collected and curated the data. DH and HX performed the statistical analysis and interpreted the data. DH drafted the manuscript. HX, JP, YX, JW and QG critically revised the manuscript for important intellectual content. JP, SL, JW and QG supervised the study. All authors read and approved the final manuscript.

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Figures

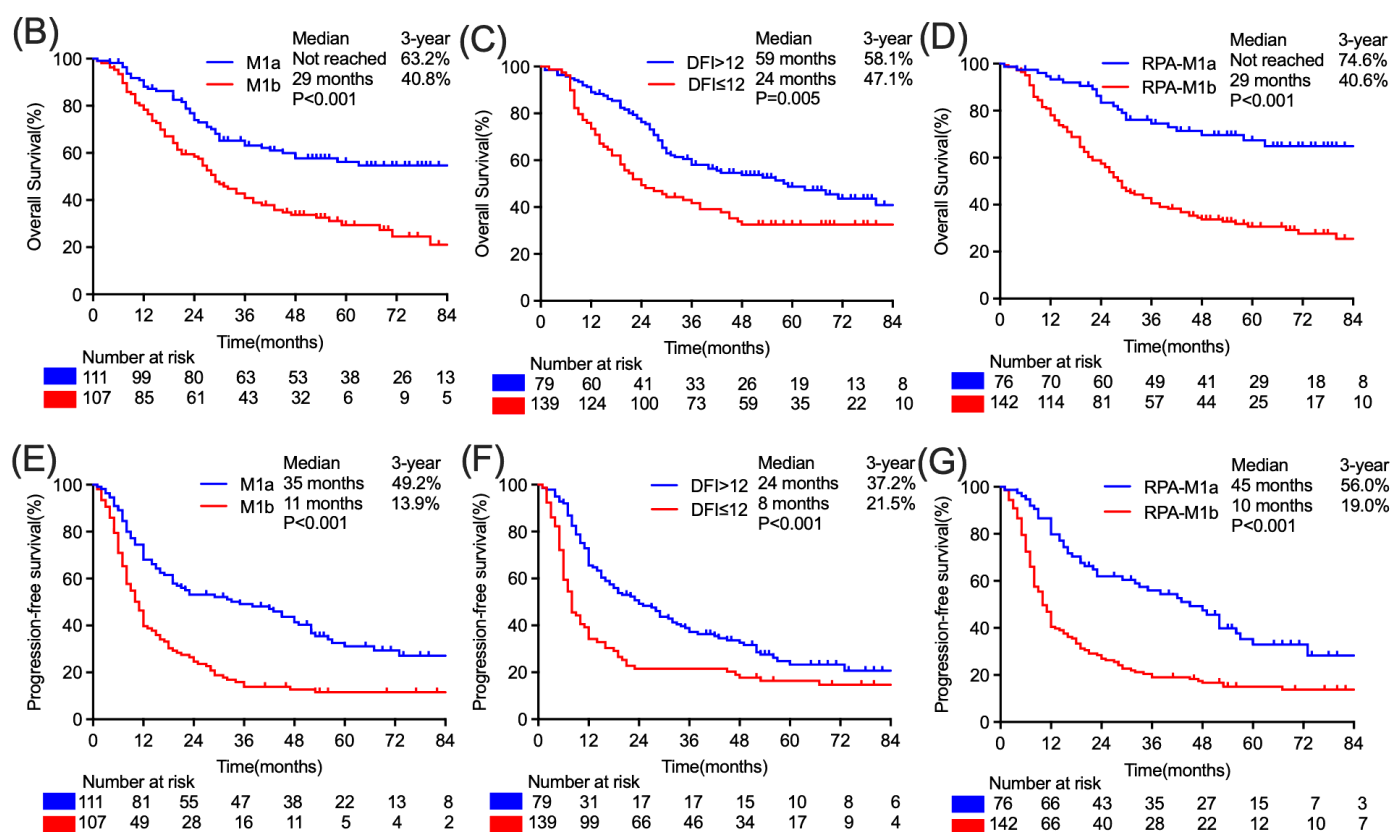
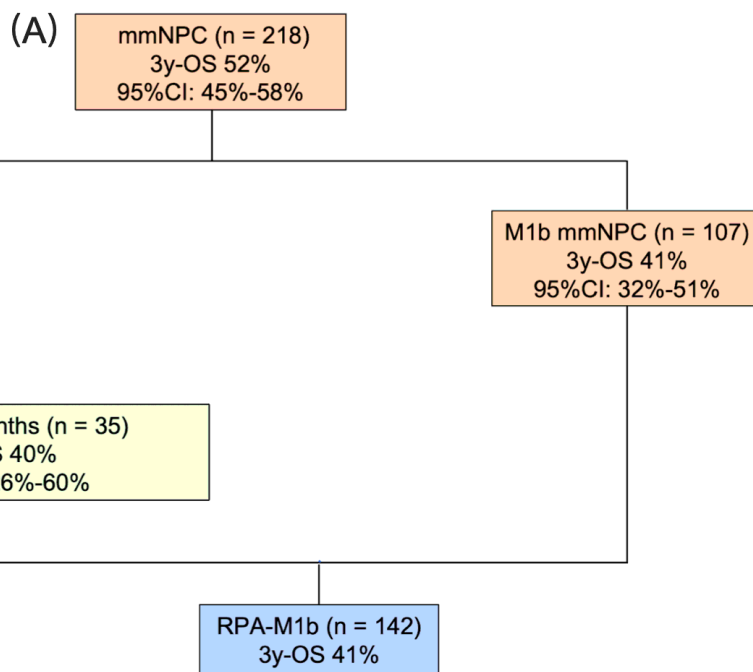


Figure 1

(A) RPA flowchart for classifying metachronous metastatic nasopharyngeal carcinoma. Kaplan–Meier estimates of OS (B–D) and PFS (E–G) by TNM-9 stage (B, E), DFI (C, F) and RPA-M1 subgroups (D, G). (Abbreviations: DFI, disease-free interval; mmNPC, metachronous metastatic nasopharyngeal carcinoma; OS, overall survival; PFS, progression free survival; RPA, recursive-partitioning analysis)

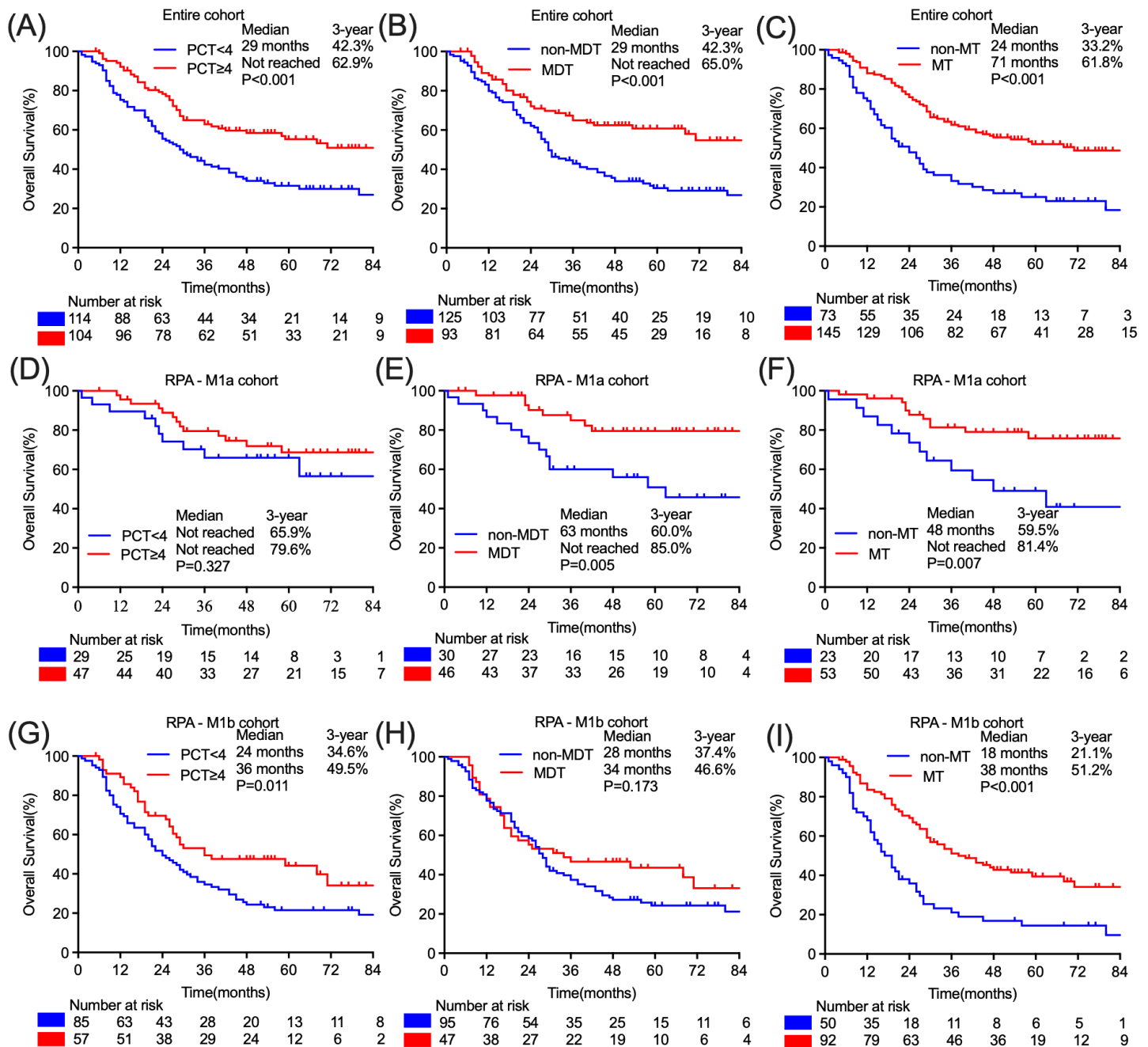


Figure 2

Kaplan–Meier estimates of overall survival by treatment modality in the entire (A–C), RPA-M1a (D–F) and RPA-M1b (G–I) cohorts. (*Abbreviations:* MDT, metastasis-directed therapy; MT, maintenance therapy; PCT, palliative chemotherapy)

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