Head & Face Medicine

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Early recurrence as a pivotal event in nasopharyngeal carcinoma: identifying predictors and key molecular signals for survivors

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Abstract

Purpose The duration of response to treatment is a significant prognostic indicator, with early recurrence (ER) often predicting poorer survival outcomes in nasopharyngeal carcinoma (NPC) survivors. This study seeks to elucidate the factors contributing to the onset of ER following radiotherapy in NPC survivors.

Methods This investigation encompassed 2,789 newly diagnosed NPC patients who underwent radical intensity-modulated radiotherapy. Ordinal logistic regression analysis was employed to evaluate the independent predictors of earlier recurrence. A machine learning-based prediction model of NPC recurrence patterns was developed. Tumorous RNA-sequencing (in-house cohort: $N = 192$) and biological tipping point analysis were utilized to infer potential molecular mechanisms associated with ER.

Results Our results demonstrated that ER within 24 months post-initial treatment was the optimal time frame for identifying early malignant progression in NPC survivors. The ER cohort (150 of 2,789, 5.38%) exhibited a notably short median overall survival of 48.6 months. Multivariate analyses revealed that male gender, T4 stage, local or regional residual disease, detectable pre- and post-radiotherapy EBV DNA, and the absence of induction chemotherapy were significant predictors of earlier recurrence. The machine learning-based predictive model further underscored the importance of tumor-related factors in NPC recurrence. Moreover, ER emerged as a pivotal stage in NPC progression, with 15 critical transition signals identified potentially associated with the negative modulation of the immune response.

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Conclusions Our comprehensive analysis of NPC recurrence patterns has unveiled insights into the key factors driving ER and provided novel insights into potential early warning biomarkers and the mechanisms underlying NPC progression.

Keywords Nasopharyngeal carcinoma, Early recurrence, Intensity modulated radiotherapy, Dynamical network biomarker, Predictive model

Introduction

Nasopharyngeal carcinoma (NPC) is a common malignant tumor of the head and neck. Radiotherapy is recommended as the main treatment for primary NPC, with chemoradiotherapy as the key to disease control and increasing the survival rate [1, 2]. Treatment for NPC continues to advance [1]. Despite the implementation of standard-of-care chemoradiotherapy, approximately 20-30% of survivors experience recurrent disease at the primary or local site, which is one of the predominant causes of treatment failure in NPC [3, 4]. As a refractory condition, recurrent NPC necessitates a multidisciplinary approach integrating expertise from various specialties, with personalized therapeutic strategies tailored to the specific clinical characteristics of each patient [5, 6]. In head and neck malignancies, the majority of tumor recurrences occur within two years post-treatment, with recurrences beyond three years being uncommon [7]. However, tumor recurrence after five years is not rare in NPC [8]. The dynamics of NPC recurrence, particularly the timing of recurrence post-treatment, significantly impact patient prognosis [9].

Post-radiotherapy, the risk of NPC recurrence demonstrates a temporal variation, typically peaking sharply at 24 months before declining [10]. Approximately 50–60% of NPC recurrences occur within this critical 24-month period [8, 9, 11]. Research indicates that a shorter interval to tumor progression is often associated with poorer survival rates across various solid malignancies [12]. In NPC, early recurrence-defined as recurrence occurring shortly after initial treatment-similarly correlates with worse survival outcomes compared to late recurrence [9]. This distinction highlights the imperative of timely identification and intervention to enhance survivors management and improve prognostic outcomes.

The biological mechanisms underlying early and late recurrence of NPC may differ and exhibit varying failure patterns and prognostic factors [13]. Cancer recurrence is influenced by a range of pathological mechanisms, including the presence of irradiation-resistant NPC cancer stem-like cells, re-proliferation of residual small lesions, substantial initial tumor burden, poor drug penetration, primary drug resistance, tumor dormancy and reactivation, as well as genetic and epigenetic alterations and immune evasion [3]. These factors may impact the time of tumor invasiveness and the biological characteristics of tumor cells. Recent research has emphasized the prognostic significance of tumor features and hematological indicators in NPC early progression [4]. However, existing studies predominantly focus on prognostic factors associated with early and late recurrence, overlooking the exploration of factors driving a more aggressive phenotype of NPC.

This study seeks to advance the understanding of NPC recurrence dynamics. Utilizing a comprehensive cohort of 2,789 NPC patients from our center, we employed ordered logistic regression and machine learning techniques to identify key factors influencing early recurrence. Additionally, we conducted a biological tipping points analysis based on transcriptome data to uncover potential molecular underpinnings of early recurrence, which are anticipated to inform the optimization of clinical surveillance strategies and deepen the understanding of malignant progression mechanisms in NPC.

Methods

Patient selection

The study cohort comprised 2,789 NPC patients who received radical intensity-modulated radiotherapy (IMRT) between January 2016 and December 2019 at Fujian Cancer Hospital, Fujian Province, China. Inclusion criteria were as follows: (1) pathologically confirmed non-metastatic NPC with well-defined staging, (2) no treatment interruptions or disease progression during the course of treatment, (3) no prior history of antineoplastic therapy, and (4) no loss to follow-up, defined as follow-up durations of at least three months from the completion of radiotherapy (excluding patients who died within three months). All patients were restaged according to the American Joint Committee on Cancer (AJCC) 8th edition TNM classification. Due to the retrospective design of the study, informed consent requirements were waived. The study received approval from the clinical research ethics committee of Fujian Cancer Hospital (K2022-030-01).

Patient assessment

Pre-treatment assessments included a comprehensive medical history, physical examination, hematological analysis, and nasopharyngoscopy with biopsy. Magnetic resonance imaging (MRI) of the head and neck was employed to evaluate the primary tumor and regional metastatic lymph nodes. For distant metastasis screening, computed tomography (CT) of the chest, abdominal

ultrasonography, and whole-body bone emission computed tomography (ECT) were utilized, with some patients undergoing ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (PET-CT) scans. The surveillance protocol were previously delineated in a prior study [14].

Treatment

All patients received IMRT at initial treatment. For those diagnosed with stage I disease, IMRT was delivered as a standalone intervention. The delineation of planning target volume (PTV) was based on the gross tumor volume of the primary nasopharyngeal tumor (GTV-T) and involved lymph nodes (GTV-N) [15]. Clinical target volume (CTV) was defined as GTV and its surrounding subclinical lesions. Prescribed radiation doses ranged from 59.36 to 78.30 Gy for PTV-GTV-T and PTV-GTV-N (1.60 to 2.53 Gy per fraction) and 48.00–66.00 Gy for PTV-CTV, delivered over 28 to 38 fractions, with treatments administered once daily, five days per week. In cases where residual lesions were identified by contrast-enhanced MRI toward the end of radiotherapy, additional irradiation (200–1000 cGy delivered over 1 to 6 fractions) was directed at residual tumor sites in the primary nasopharynx or metastatic lymph nodes, as clinically indicated. The dose limits for organs at risk and the assessment of the treatment plan were established in line with the Radiation Therapy Oncology Group 0225 protocols [16]. Patients with stage II to IVa disease were treated with IMRT alone or concurrent chemoradiotherapy, in combination with or without induction chemotherapy or adjuvant chemotherapy. Induction and adjuvant chemotherapy regimens commonly included gemcitabine, paclitaxel, 5-fuorouracil or other regimens, combined with platinum-based agents every 3 weeks. Concurrent chemotherapy during radiotherapy typically consisted of cisplatin or other platinum compounds, administered in 3-week cycles.

Salvage treatments were decided based on a multidisciplinary team (MDT) discussion and the patient's intentions. The salvage regional treatments included reirradiation and salvage surgeries, including radical or selective neck dissection and the nasopharyngectomy. Reirradiation with IMRT was suitable for irresectable deseases but the interval between the first and second courses of IMRT should be ≥1 year. Chemotherapy and immunotherapy were used as systemic treatments. The chemotherapy regimens for recurrence was mainly platinum combined with paclitaxel, docetaxel, gemcitabine, or 5-fluorouracil.

Definition of recurrence stage

Local recurrence was defined as the initial detection of a new pathologically confirmed tumor at least six months post-radiotherapy, confirmed either through biopsy of the primary lesion or fine-needle aspiration of metastatic lymph nodes. For lesions inaccessible to direct sampling, clinical diagnosis required the presence of at least two distinctive radiological features. To establish a definitive definition of recurrence stage in NPC, we first conducted a comprehensive review of existing studies on early recurrence in NPC, summarized in Table 1. Subsequently, in conjunction with the peak recurrence periods in our cohort, we evaluated the applicability of two commonly employed recurrence time points for identifying dynamic risk, including ER24, indicating early recurrence within 24 months of initial treatment, and ER36, indicating recurrence within 36 months. Survivors were subsequently categorized into non-recurrence (NR), early

Table 1 Definitions of early recurrence for NPC in different studies

ER definitions	Reference	Patient resources	Results of ER population	Independent risk factors in ER population
The time to tumor recurrence ≤ 24 months after treatment	Zhang, 2022[3]	Sun Yat-sen University Cancer Center, China	Early progression: 1027/1953 (52.59%); 5-year OS: 31.9 months	T stage, N stage, gender, age, WHO histologic type, CRP, ALB, LDH, EBV DNA load, and cigarette consumption.
	Chen, 2022[5]	Kaohsiung Chang Gung Memorial Hospital	315/533 (59.10%); Median OS: 1.8 years, median DSS: 2.1 years.	NA
	Li, 2020[6]	Sun Yat-sen University Cancer Center, China	462/916 (50.44%); OS, NA	Age and gender for OS in the purely local ER group; Alcohol abuse and TNM stage for OS in the purely regional ER group; N stage and TNM stage for OS in the purely locoregional ER group.
	Chee, 2016[8]	Department of Otolaryngology - Head and Neck Surgery, National University Health System, Singapore	NA	NA

ALB, albumin; *CRP*, C-reactive protein; *DSS*, disease-specific survival; *EBV DNA*, Epstein-Barr virus DNA; *ER*, early recurrence; *LDH*, lactate dehydrogenase; *NA*, not applicable; *NPC*, nasopharyngeal carcinoma; *OS*, overall survival; *WHO*, World Health Organization

recurrence (ER), and late recurrence (LR) groups based on the time to recurrence (TTR).

Machine learning models

Two classifiers, random forest (RF) and light gradient boosting machine (LightGBM) from the "rtemis" R package, were employed to construct a supervised predictive model for NPC recurrence patterns [17]. The prediction performance of these machine learning models was assessed using a five-fold cross-validation approach. For each model, automatic parameter tuning was performed using the built-in functionality of the "rtemis" package. The significance of various features within the models was illustrated through top important feature panels generated by the different algorithms. Sensitivity, specificity, positive predictive value (PPV) for high-risk group and negative predictive value (NPV), balanced accuracy, and confusion matrix were used to evaluate the model.

Biological tipping points analysis

To elucidate the underlying dynamical mechanism of NPC progression, we utilized transcriptome data from 192 NPC cases (Fujian cohort) previously reported to investigate temporal features of gene-regulatory network dynamics at phenotypically defined key points, which could be exploited to infer key factors that play a role in early recurrence [18, 19]. Patient characteristics and RNA sequencing details have been outlined in our recent publications [19]. Biological tipping points analysis was conducted using the R package "BioTIP", involving three primary steps: construction of gene network partitions, identification of putative critical transition signals (CTSs), and evaluation of tipping points and CTSs [20]. The expression matrix was derived from the original FPKM values and log2-transformed for normalization. Gene networks were constructed using the "getNetwork" function, with a minimum module size parameter set to 10 genes. The "getMCI" function was employed to compute the module-criticality index (MCI) for each gene module, facilitating the identification of putative CTSs. Each gene module, representing a highly correlated dynamic molecular subnetwork in the pre-disease state-also referred to as a dynamical network biomarker (DNB)-can act as an effective early-warning signal for disease state transitions [18]. Subsequently, the index of critical transition (Ic.shrink score) was calculated to evaluate the identified CTSs. To assess the robustness of these CTSs, a bootstrap analysis was conducted using randomly selected gene sets, each comprising the same number of members as the dominant group. Other detailed theoretical foundation and computational algorithm for "BioTIP" analysis were described elsewhere [20]. Gene Ontology (GO) enrichment analysis was performed to explore the biological functions of CTSs, with a significance threshold set at a p-value of 0.05. The top five enriched pathways were selected for visualization.

Statistical analysis

Statistical analyses were conducted using SPSS Statistics (version 25.0) and R (version 4.3.0), with additional support from Zstats v0.90 (www.medsta.cn/software). The study incorporated covariates included age, gender, TNM stage, plasma Epstein-Barr virus (EBV) DNA levels, residual disease after radiotherapy, and the use of induction, concurrent, and adjuvant chemotherapy. Pre-treatment EBV DNA levels were categorized dichotomously using a threshold of 4,000 copies/mL, previously established as indicative of a "high-risk" profile for disease progression [21]. Age was analyzed as a categorical variable based on the median value. Both pre- and post-radiotherapy EBV DNA levels (detectable vs. undetectable) were also analyzed categorically. Missing data for plasma EBV DNA levels were addressed using multiple imputations via the "MICE" R package [22]. Residual disease is defined as the confirmation of disease within 6 months post-treatment. Disease identified after this period, following a prior complete remission, was classified as recurrence. Overall survival (OS) was calculated from the end of radiotherapy to the date of death or the last follow-up. To assess the impact of ER on survival outcomes more comprehensively, three additional prognostic metrics were defined: OS from recurrence, calculated from the date of the first recurrence to death or the last follow-up; OS from landmark, defined as the interval from the ER cutoff to death or the last follow-up; and adjusted OS, which differentiates OS from recurrence for the ER group and OS from landmark for the reference group. Baseline characteristics were compared using the Chi-squared test. Survival curves were generated using the Kaplan-Meier method and compared with the log-rank test, adjusted by the Bonferroni correction. Cox proportional hazards regression analysis was employed to evaluate the prognostic impact of ER. To identify predictors of early recurrence, an ordinal logistic regression model was applied based on recurrence status (NR, LR, ER), with variables showing p-value <0.05 being further examined in a multivariate logistic regression model. A significance threshold of p-value <0.05 was adopted for all analyses.

Results

Study population and recurrence distribution

The study encompassed a cohort of 2,789 NPC patients, with a median age of 49 years (range, 10 to 87 years). Of the total cohort, 10.11% ($N=282$) experienced recurrence, with a median follow-up duration of 55.8 months (interquartile range, 43.4–67.2 months). The rates of local recurrence (including retropharyngeal lymph nodes), regional lymph node recurrence, and combined local

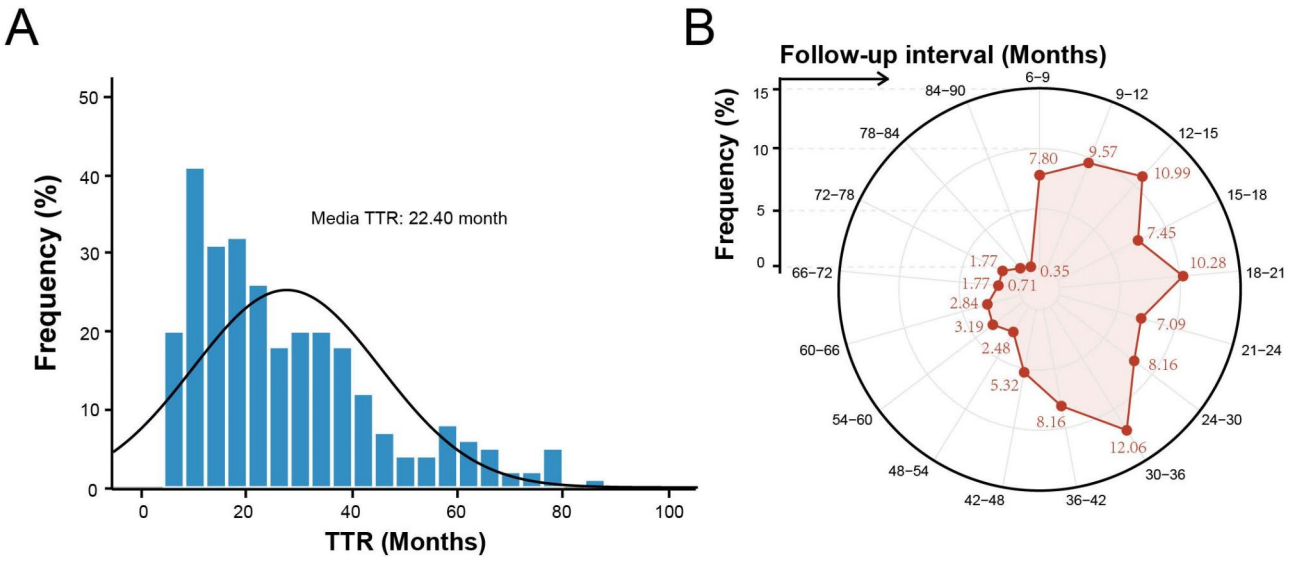

Fig. 1 Recurrence rate of patients with nasopharyngeal carcinoma. (**A**) Frequency distribution histogram for recurrence in NPC patients. (**B**) The proportion of patients with recurrent NPC every 3–6 months. NPC, nasopharyngeal carcinoma; TTR, time to recurrence

Table 2 The prognostic impacts on overall survival of two different early recurrence timepoints and different early recurrence definitions under diverse choices of chemotherapy patterns

Variables	HR (95% CI)	*p*-value
ER24 vs. Reference	12.330 (9.476–15.184)	< 0.001
ER36 vs. Reference	8.704 (6.260-11.148)	< 0.001
ER24 analysis		
Population with inducing chemotherapy	12.249 (9.288–15.210)	< 0.001
Population with concurrent chemotherapy	8.842 (5.401–12.282)	< 0.001
Population with adjuvant chemotherapy	11.926 (3.112–20.741)	0.009
ER36 analysis		
Population with inducing chemotherapy	11.177 (7.865–14.488)	< 0.001
Population with concurrent chemotherapy	5.556 (2.667–8.444)	< 0.001
Population with adjuvant chemotherapy	5.833 (-2.054-13.719)	0.148

ER24, early recurrence within 24 months after radical radiotherapy; *ER36*, early recurrence within 36 months after radical radiotherapy

and regional lymph node recurrence were 5.20%, 3.76%, and 1.15%, respectively. The nasopharynx was the most common site of recurrence, with local anatomical sites including the parapharyngeal space, pterygomaxillary fossa, and skull base. The locoregional recurrence rates at 1 year, 3 years, and 5 years were 1.76%, 7.42%, and 9.36%, respectively.

We summarized the existing studies on early recurrence in NPC and found that recurrence within 24 months from the initial radiotherapy is frequently used to define ER (Table 1). In our cohort, the peak risk of recurrence similarly occurred around 24 months post-treatment (Fig. 1A). However, routine follow-up data revealed that most local recurrences (73.76%, 208/282) were observed within the first 36 months after treatment completion, aligning with findings reported by Chen et al. (Fig. 1B) [23]. We evaluated the prognostic significance of two ER time points-24 months and 36 months-in our patient cohort, assessing their impact on mortality risk following various treatments (Table 2). Our results indicated that using a 24-month ER time point yielded more robust results, effectively mitigating biases associated with ER definitions across different chemotherapy regimens. Consequently, 150 patients were categorized into the ER group, while 132 were assigned to the LR group.

Following recurrence, 220 patients (78.01%) underwent salvage therapy, whereas 62 patients (21.99%) did not receive additional treatment at our center. Among 220 patients, 63 patients (28.64%) underwent surgery alone, 55 (25%) received reirradiation with or without chemotherapy, 4 (1.82%) underwent surgery in combination with reirradiation, and 14 (6.36%) were treated with reirradiation and immunotherapy. In patients treated with reirradiation alone, the median radiation dose was 64 Gy (range, 54–70.95 Gy). Additionally, 41 patients (18.64%) received chemotherapy, 29 (13.18%) underwent combined chemotherapy and immunotherapy, 13 (5.90%) received immunotherapy alone, and one patient with recurrence in retropharyngeal lymph node received interstitial brachytherapy.

Patient characteristics and clinical treatment outcome

Demographics and clinical characteristics of patients with ER, LR and non-recurrence NPC are summarized in Table 3. This cohort included 2,020 male patients and 769 female patients, yielding a male-to-female ratio of 2.63:1. Post-radiotherapy, 79.85% (2,227/2,789) of patients achieved complete remission, while 20.15% (562/2,789) attained partial remission Among those with partial remission, 42.70% (240/562) exhibited detectable primary tumor residue (including retropharyngeal lymph nodes), 33.10% (186/562) had residual cervical lymphatic lesions, and 24.20% (136/562) presented with both primary tumor and cervical lymphatic lesion residue. Compared to the NR group, the patients with recurrent

Table 3 Baseline characteristics of patients with early recurrence, late recurrence and non-recurrence NPC

Characteristic	Total *N* = 2789	NR group *N* = 2507	LR group *N* = 132	ER group *N* = 150	*p*-value		
					NR vs. LR	NR vs. ER	LR vs. ER
Age, *N* (%)					0.785	0.436	0.451
< 50 years old	1474 (52.85)	1322 (52.73)	68 (51.52)	84 (56.00)			
≥ 50 years old	1315 (47.15)	1185 (47.27)	64 (48.48)	66 (44.00)			
Gender, *N* (%)					0.069	0.003	0.409
Male	2020 (72.43)	1792 (71.48)	104 (78.79)	124 (82.67)			
Female	769 (27.57)	715 (28.52)	28 (21.21)	26 (17.33)			
T stage, *N* (%)					0.078	0.004	0.382
T0-1	533 (19.11)	491 (19.59)	20 (15.15)	22 (14.67)			
T2	482 (17.28)	446 (17.79)	15 (11.36)	21 (14.00)			
T3	1102 (39.51)	990 (39.49)	59 (44.70)	53 (35.33)			
T4	672 (24.09)	580 (23.14)	38 (28.79)	54 (36.00)			
N stage, *N* (%)					0.156	0.128	0.760
N0	212 (7.60)	202 (8.06)	4 (3.03)	6 (4.00)			
N1	1105 (39.62)	999 (39.85)	53 (40.15)	53 (35.33)			
N2	960 (34.42)	849 (33.87)	52 (39.39)	59 (39.33)			
N3	512 (18.36)	457 (18.23)	23 (17.42)	32 (21.33)			
Clinical stage, *N* (%)					0.452	0.004	0.314
Stage I	61 (2.19)	57 (2.27)	2 (1.52)	2 (1.33)			
Stage II	363 (13.02)	339 (13.52)	12 (9.09)	12 (8.00)			
Stage III	1251 (44.85)	1133 (45.19)	62 (46.97)	56 (37.33)			
Stage IV	1114 (39.94)	978 (39.01)	56 (42.42)	80 (53.33)			
EBV $DNA_{pre-treatment}$, *N* (%)					0.817	0.003	0.026
≤ 4000 copies/mL	1645 (58.98)	1494 (59.59)	80 (60.61)	71 (47.33)			
> 4000 copies/mL	1144 (41.02)	1013 (40.41)	52 (39.39)	79 (52.67)			
EBV DNA_{pre-RT}, *N* (%)					0.002	< 0.001	0.421
Undetectable	1341 (48.08)	1247 (49.74)	47 (35.61)	47 (31.33)			
Detectable	1448 (51.92)	1260 (50.26)	85 (64.39)	103 (68.67)			
EBV $DNA_{post-RT}$, *N* (%)					< 0.001	0.045	0.057
Undetectable	2367 (84.87)	2154 (85.92)	93 (70.45)	120 (80.00)			
Detectable	422 (15.13)	353 (14.08)	39 (29.55)	30 (20.00)			
Received inducing chemotherapy, *N* (%)					0.047	0.007	0.591
No	410 (14.70)	387 (15.44)	12 (9.09)	11 (7.33)			
Yes	2379 (85.30)	2120 (84.56)	120 (90.91)	139 (92.67)			
Received concurrent chemotherapy, *N* (%)					0.105	0.914	0.186
No	854 (30.62)	775 (30.91)	32 (24.24)	47 (31.33)			
Yes	1935 (69.38)	1732 (69.09)	100 (75.76)	103 (68.67)			
Received adjuvant chemotherapy, *N* (%)					0.125	0.205	0.823
No	2530 (90.71)	2283 (91.07)	115 (87.12)	132 (88.00)			
Yes	259 (9.29)	224 (8.93)	17 (12.88)	18 (12.00)			
Residue, *N* (%)					0.003	< 0.001	0.572
No	2227 (79.85)	2033 (81.09)	93 (70.45)	101 (67.33)			
Yes	562 (20.15)	474 (18.91)	39 (29.55)	49 (32.67)			

Categorical data were represented as number with percentage with Chi-squared test. *EBV DNA*, Epstein-Barr virus DNA; *ER*, early recurrence; *LR*, late recurrence; *NPC*, nasopharyngeal carcinoma; *NR*, non-recurrence; *RT*, radiotherapy

NPC exhibited significantly higher levels of detectable pre-RT (NR vs. LR, $p=0.002$; NR vs. ER, $p<0.001$) and post-RT plasma EBV DNA (NR vs. LR, $p<0.001$; NR vs. ER, $p=0.045$). Additionally, a greater proportion of these patients had local or regional residues following radiotherapy (NR vs. LR, $p=0.003$; NR vs. ER, $p<0.001$). Patients with ER were more likely to be male (82.67% vs. 71.48%, $p=0.003$), present with advanced initial T stage ($p=0.004$), have advanced AJCC staging at diagnosis ($p=0.004$), and exhibit higher pre-treatment plasma EBV DNA levels (52.67% vs. 40.41%, $p=0.003$) compared to those in the NR group. Furthermore, the proportion of patients with pre-treatment EBV DNA levels exceeding 4,000 copies/mL was higher in the ER group compared to the LR group (52.67% vs. 39.39%, $p=0.026$). Initial treatment patterns across the three groups were relatively balanced, with only the use of induction chemotherapy showed a significant difference between the recurrence and non-recurrence groups (NR vs. LR, $p=0.047$; NR vs. ER, $p=0.007$).

Survivors in the ER group demonstrated a significantly higher risk of mortality, with a median OS of 48.6 months compared to the NR (HR: 6.612, 95% CI: 3.999–10.932, adjust log-rank $p<0.001$) and LR group (HR: 3.878, 95% CI: 2.673–5.625, adjust log-rank $p<0.001$), where median OS was not reached (Fig. 2A). Additionally, the LR group also had shorter OS compared to the NR group (HR: 1.787, 95% CI: 1.104–2.894, adjusted log-rank $p=0.007$). Given that ER was defined as a time-dependent endpoint (24 months), we further evaluated additional survival metrics between the ER and LR cohorts. The OS from landmark analysis revealed similar patterns, with the ER group having an OS of 50.67 months compared to not reached in the LR group (HR: 2.782, 95% CI: 1.789–4.325, $p<0.001$; Fig. 2B). OS from recurrence also showed that the ER group had an OS of 32.63 months versus not reached in the LR group (HR: 1.810, 95% CI: 1.243–2.637, adjusted log-rank $p=0.004$; Fig. 2C). The adjusted OS in ER population was 32.63 months, significantly shorter than those patients in reference group (not reach, HR: 3.226, 95% CI: 2.233–4.661, adjust log-rank $p<0.001$, Fig. 2D).

Risk factors of earlier recurrence

We next explored risk factors for earlier recurrence in NPC survivors based on baseline clinical characteristics and therapeutic variables. An ordinal logistic regression model was constructed with recurrence status (non-recurrence [NR], late recurrence [LR], early recurrence [ER]) as the dependent variable. The correlation matrix indicated no significant multicollinearity among variables (variance inflation factors were all below 2), and the Brant test confirmed that the parallel regression assumption was met ($p>0.05$). Univariate analysis identified several factors associated with ER, including male gender, T4 stage, advanced N stage, pre-treatment EBV DNA levels>4,000 copies/mL, detectable pre- and post-radiotherapy EBV DNA, local or regional residual disease after radiotherapy, and the absence of induction chemotherapy. These variables were subsequently included in the multivariate analysis. Finally, male gender (female vs. male, OR: 0.607, 95% CI: 0.444–0.831, $p=0.002$), T4 stage (OR: 1.552, 95% CI: 1.019–2.365, $p=0.041$), local or regional residue after RT (OR: 1.739, 95% CI: 1.315-2.300, $p<0.001$), detectable pre-RT (OR: 1.786, 95% CI: 1.349–2.365, $p<0.001$) and post-RT EBV DNA (OR: 1.460, 95% CI: 1.063–2.006, $p=0.020$), maintained their independent predictors for earlier recurrence (Table 4). Patients who achieved induction chemotherapy in initial treatment also had a reduced risk of earlier recurrence (without induction chemotherapy vs. with induction chemotherapy: OR: 1.712, 95% CI: 1.023–2.868, $p=0.041$).

Machine learning-based prediction of NPC recurrence patterns

We postulated that a holistic integration of clinical features could provide important clues to predict NPC recurrence outcomes. Therefore, we included all clinical features including age (>50 years old and ≤50 years old), gender, T stage, N stage, pre-treatment EBV DNA (>4000 copies/mL vs. ≤ 4000 copies/mL), pre-RT and post-RT EBV DNA (detectable vs. undetectable), residue after radiotherapy, as well as the use of induction, concurrent and adjuvant chemotherapy, all of which were used for the development of predictive models for NPC recurrence patterns. Our findings indicated that the RF model provided better discrimination performance, with sensitivity, specificity, accuracy, PPV, and NPV of 84.64%, 90.19%, 87.41%, 50.18%, and 75.38%, respectively (Fig. 3A, S1 Table). To elucidate the contribution of individual features to the RF-based predictive model, we assessed the importance of each predictor. T stage and N stage emerged as the most significant variables in both models (Fig. 3B), highlighting that tumor-related factors remain paramount in predicting NPC recurrence.

Characterizing the critical transition signals for earlier recurrence

We hypothesize that distinct gene expression profiles characterize each recurrence state (NR, LR, or ER), reflecting different molecular phenotypes. To explore the molecular mechanisms underlying recurrence state transitions in NPC survivors, we conducted a biological tipping points analysis. This analysis included 181 non-metastatic NPC patients from the Fujian cohort, categorized into three groups based on the defined criteria for early recurrence: 162 patients in the NR group, 11 in the LR group, and 8 in the ER group. After constructing gene

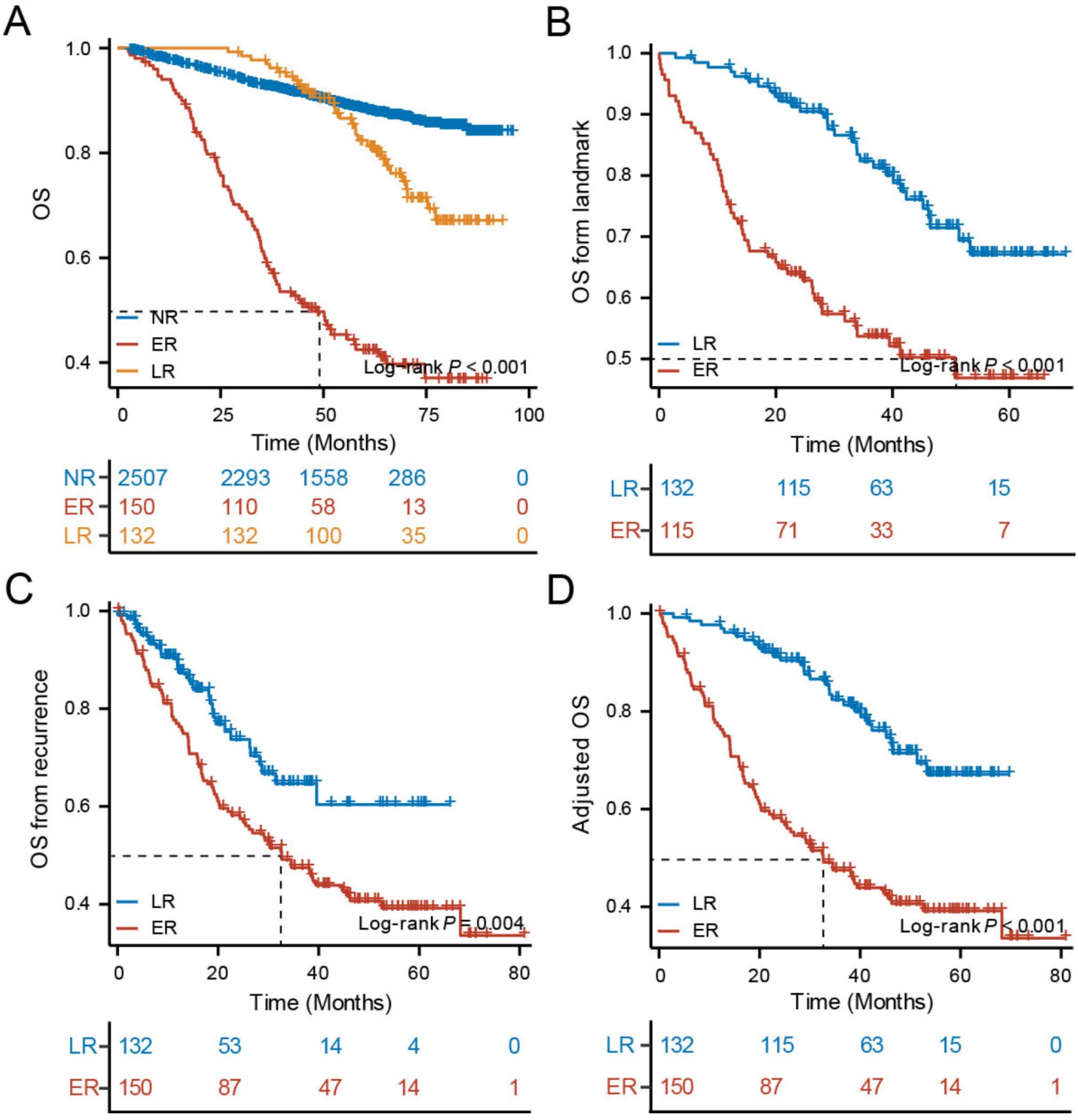

Fig. 2 The adverse impact of ER24 on prognosis. The (**A**) OS, (**B**) OS from landmark, (**C**) OS from progression, and (**D**) adjusted OS of patients in ER24 analysis. ER, early recurrence; ER24, early recurrence within 24 months after radical radiotherapy; LR, late recurrence; NR, non-recurrence; OS, overall survival

network partitions and calculating the MCI, a group of 72 genes is identified as CTSs in NR group, 15 genes in ER group, and 62 genes in LR group (S2 Table). As depicted in Fig. 4A, the index of critical transition for CTSs (represented by the red curve) markedly increased in the ER status, indicating that ER represents a pivotal stage in NPC progression. Bootstrap validation (illustrated by the blue curves) confirmed that randomly selected gene sets of the same size as the CTSs were insensitive to critical transition, further demonstrating the robustness of 15 genes as CTSs in ER group. 15 CTSs included *CST7*, *GPR31*, *GTSF1L*, *IL4I1*, *ISG20*, *KCNAB2*, *NME8*, *OTOF*, *RNASET2*, *SP140*, *SPI1*, *SSTR3*, *SYN1*, *WAS*, and *ZBTB32*. The top five GO biological process enrichment pathways for these CTSs were associated with negative regulation of leukocyte activation, response to tumor cell, negative regulation of cell activation, regulation of leukocyte mediated immunity, and negative regulation of

Table 4 The association between clinical characteristics and earlier recurrence for NPC patients by ordered logistic regression

Variables	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years, < 50 vs. ≥ 50)	0.949 (0.742–1.215)	0.680		
Gender (female vs. male)	0.591 (0.434–0.805)	< 0.001	0.607 (0.444–0.831)	0.002
T stage				
T0-1	1.000 (Reference)		1.000 (Reference)	
T2	0.948 (0.597–1.507)	0.822	0.868 (0.541–1.390)	0.555
T3	1.314 (0.907–1.903)	0.148	1.205 (0.805–1.805)	0.364
T4	1.868 (1.273–2.742)	0.001	1.552 (1.019–2.365)	0.041
N stage				
N0	1.000 (Reference)		1.000 (Reference)	
N1	2.128 (1.094–4.139)	0.026	1.744 (0.885–3.438)	0.108
N2	2.629 (1.352–5.110)	0.004	1.951 (0.975-3.900)	0.059
N3	2.435 (1.217–4.872)	0.012	1.719 (0.822–3.596)	0.150
$EBV\ DNA_{pre-treatment}$ (copies/mL, > 4000 vs. ≤ 4000)	1.298 (1.014–1.662)	0.038	0.956 (0.731–1.250)	0.742
$EBV\ DNA_{pre-RT}$ (detectable vs. undetectable)	1.986 (1.532–2.574)	< 0.001	1.786 (1.349–2.365)	< 0.001
$EBV\ DNA_{post-RT}$ (detectable vs. undetectable)	1.927 (1.438–2.583)	< 0.001	1.460 (1.063–2.006)	0.020
Induction chemotherapy (no vs. yes)	2.061 (1.328-3.200)	0.001	1.712 (1.023–2.868)	0.041
Concurrent chemotherapy (no vs. yes)	1.139 (0.867–1.496)	0.351		
Adjuvant chemotherapy (no vs. yes)	1.438 (0.984–2.099)	0.060		
Residue (no vs. yes)	1.951 (1.489–2.556)	< 0.001	1.739 (1.315-2.300)	< 0.001

EBV, Epstein-Barr virus; *NPC*, nasopharyngeal carcinoma; *OR*, odds ratio; *RT*, radiotherapy

leukocyte mediated immunity, suggesting a potential link to immune system dysregulation (Fig. 4B).

Discussion

Herein, we utilized substantial cohort of 2,789 NPC patients to assess the incidence and long-term survival outcomes associated with ER and LR following definitive treatment. The large sample size and long follow-up time enhances the statistical power and the generalizability of the findings. We identified that the ER within 24 months as a demarcation for early malignant progression of NPC, with early recurrence being a significant predictor of poor prognosis. We identified key predictors of early recurrence and developed a machine learning-based predictive model leveraging these tumor-related factors. Additionally, by integrating NPC transcriptome data from our institution, we investigated critical transition signals underlying the transformation to ER. The identification of key predictors and molecular signals for early recurrence could lead to the development of targeted surveillance strategies and personalized treatment plans, which would have significant implications for clinical practice and offer novel insights into the mechanism of NPC deterioration.

IMRT has increasingly supplanted 2D and 3D conformal radiotherapy as the standard treatment for NPC, significantly enhancing patient prognosis [24]. Nevertheless, local/regional recurrence and distant metastasis continue to be leading causes of treatment failure [3]. Notably, the incidence of NPC treatment failure peaks within 2 years and then gradually declines, with up to over 50% of recurrence and metastasis events occurring within this period [4, 10]. This also echoes the stronger frequency and intensity of follow-up in the first 2 years of NPC [25]. Several studies have identified the 24-month post-initial treatment time point as the definition for ER and have documented poorer survival outcomes for ER patients [9, 12]. Our study showed that 10.11% patients developed recurrence, with 53.18% occurred within the first 2 years, which is in line with previous research. Furthermore, using a 24-month definition of ER maintained a significant prognostic effect in a diverse group of patients receiving chemotherapy, confirming its utility. Patients with ER face notably adverse outcomes, with a median overall survival of approximately 32 months following recurrence, highlighting the critical need for timely identification and early intervention strategies.

Recurrence in NPC remains a challenging issue with multifaceted management hurdles [6]. The primary therapeutic avenue, nasopharyngectomy, is the treatment of choice if anatomically feasible, predominantly performed through either an open or more prevalent endoscopic route [26]. Nonetheless, surgical intervention maintains viability solely for smaller recurrent lesions situated in accessible regions [27]. For the bulk of patients with recurrent disease unsuitable for surgery, re-irradiation

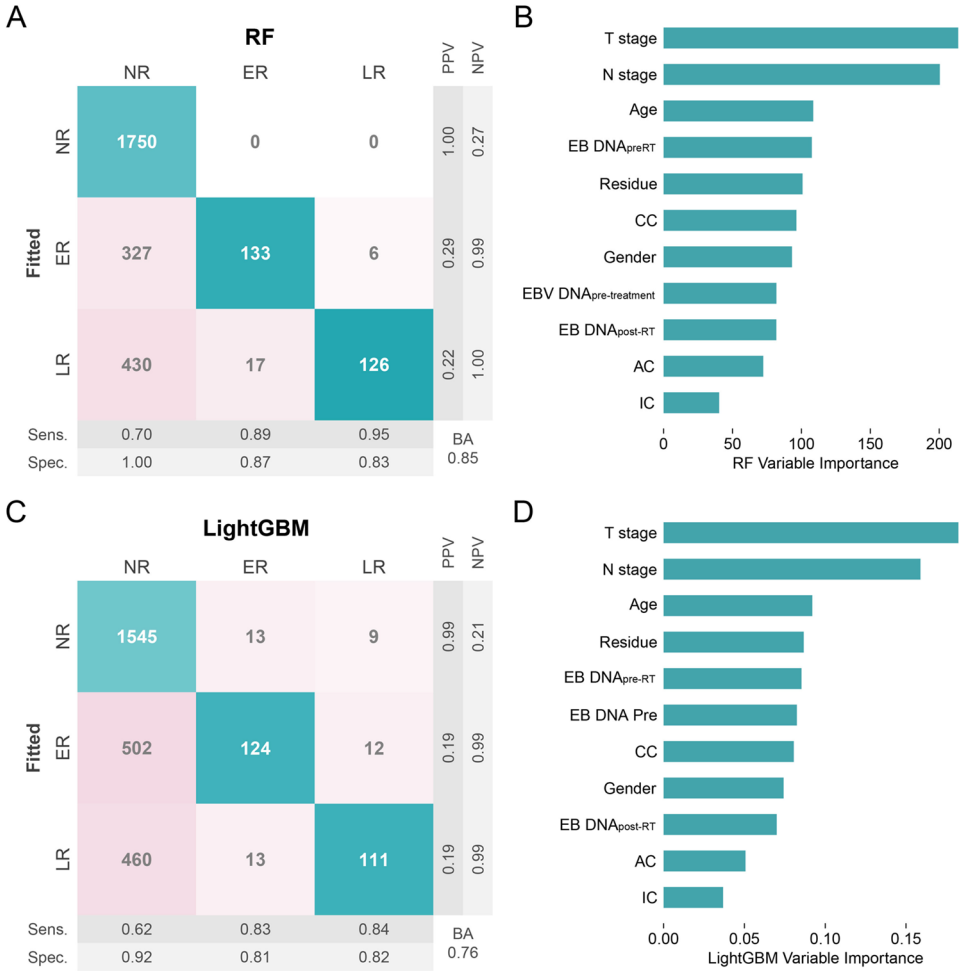

Fig. 3 Predictive model for early recurrence of nasopharyngeal carcinoma. Confusion matrix (A, C) and the most important features for the prediction of NPC recurrence (B, D) in RF and LightGBM model. AC, adjuvant chemotherapy; BA, balanced accuracy; CC, concurrent chemotherapy; EBV DNA, Epstein-Barr virus DNA; ER, early recurrence; IC, inducing chemotherapy; LightGBM, light gradient boosting machine; LR, late recurrence; NPV, negative predictive value; NR, non-recurrence; PPV, positive predictive value; RF, random forest; RT, radiotherapy

stands as a potential recourse, offering a renewed opportunity for remission [28]. Optimal results hinge on meticulous patient selection and appropriate re-radiotherapy dosing and scheduling [29]. Our previous study showed that patients with higher age at recurrence and advanced rT category could benefit from salvage RT alone [30]. You et al. found the efficacy of hyperfractionated IMRT in decreasing severe late complications and improving OS in patients grappling with locally advanced recurrent NPC that could be used as the standard of care for these patients [31]. Tagliaferri et al. found the combination of endoscopy and brachytherapy is also a safe option for treating recurrent nasopharyngeal tumors [32]. Moreover, anti-PD-1/PD-L1 immunotherapy has emerged as a propitious strategy, promising to uplift patient prognoses and improve NPC management [33]. The administration of toripalimab in conjunction with gemcitabine-cisplatin has emerged as the first-line therapeutic regimen for this subset of patients in need [34]. In this cohort, salvage surgery and re-irradiation remained the primary therapeutic strategies for recurrent NPC, and the application of immunotherapy is also gradually increasing. As the prognosis of NPC has progressively improved in recent years, clinicians are placing greater emphasis on identifying patients who may benefit from effective treatment for recurrent tumors, with the aim of achieving long-term survival [35]. However, due to the heterogeneity in treatment approaches and the limited sample size within each treatment subgroup, we were unable to determine which patients would derive the most benefit from local or systemic therapies based on time to recurrence. Optimal treatment strategies for recurrent nasopharyngeal carcinoma should be determined through multidisciplinary team discussions [2].

The duration of response is critical in the progression of NPC [11]. However, the timing of recurrence varies from individual to individual. One potential explanation is the presence of dormant cells within tumors, which

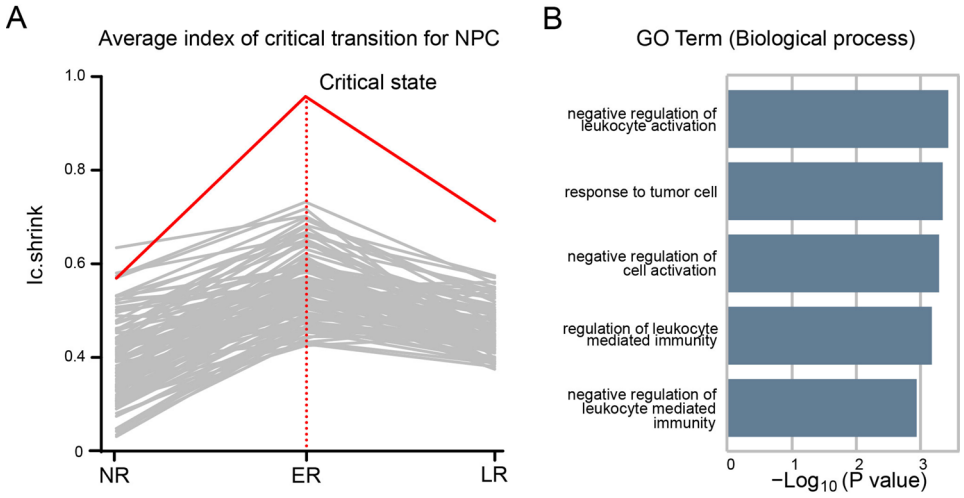

Fig. 4 Identification of critical states for tumor deterioration in NPC. (**A**) The index of critical transition (lc.shrink score) of different recurrent patterns. The lc.shrink scores for the identified dominant group (red curve) and random verification groups from bootstrap (blue curves). (**B**) Enriched GO pathways of biological process for identified 15 critical transition signals in ER status. ER, early recurrence; GO, Gene Oncology; LR, late recurrence; NPC, nasopharyngeal carcinoma; NR, non-recurrence

may become activated under specific conditions, leading to enhanced invasion and metastasis [36]. Another probable hypothesis involves the varying radiosensitivity of NPC tumor cells [37]. Recent research has implicated factors such as apoptosis, DNA damage repair, hypoxic microenvironments, and autophagy in the modulation of radiotherapy resistance, which may contribute to variations in early and late recurrence [3]. This suggests intrinsic biological differences between patients with early and late recurrence, meriting further investigation. Additionally, tumor-related features may also contribute to the variability in recurrence timing [4]. A recent study investigating prognostic factors for early and late recurrence in NPC, however, they found no correlation between post-recurrence OS and the timing of recurrence [9]. In our analysis, we observed that patients with T4 stage NPC, local or regional residue, detectable pre- and post-radiotherapy EBV DNA, and those who did not receive induction chemotherapy were more prone to earlier recurrence. It's known that the TNM staging system, a primary tool for prognostic evaluation and therapeutic guidance, is strongly associated with disease progression [38]. T4 stage NPC is characterized by a high tumor burden and intracranial extension and/or cranial nerve involvement [38]. The constraints on radiation delivery to critical neural structures, such as the spinal cord and brainstem, may result in suboptimal radiation coverage and dosing, potentially leading to tumor recurrence [39]. It has established that the presence of residual tumor correlates with an increased risk of recurrence and poorer survival outcomes [11]. In addition, evidence on plasma EBV DNA has consistently linked baseline or posttreatment levels, as well as their trends, to patient outcomes [40]. However, there is no consensus on the precise assessment of biochemical response. Most studies define optimal EBV DNA response as posttreatment clearance, with baseline thresholds ranging from 500 to over 4000 copies/mL [21]. Dynamic measures might be better suited to offer a more comprehensive evaluation of treatment response [40].

Artificial intelligence (AI), an emerging discipline within the field of science, has demonstrated considerable potential across various clinical applications for NPC, particularly in leveraging medical imaging and clinical data to streamline workflows and predict patient outcomes [41, 42]. A subset of AI, machine learning, excels in capturing nonlinear relationships and conditional dependencies within data, offering high accuracy and adaptability when applied to clinical research datasets [43]. In previous research, we employed machine learning to develop a predictive model for parotid mucoepidermoid carcinoma [44]. In this study, we found that T stage had the highest impact on earlier recurrence within a machine learning model. By integrating clinical factors and hematological indicators EBV DNA to construct predictive models, machine learning algorithms provide a powerful framework for complex models that are able to predict the risk of recurrence in NPC survivors [42]. Nevertheless, the limited number of recurrent cases poses a challenge in establishing an independent validation set. We look forward to more future large-scale, multicenter studies of high quality to further validate our findings and enhance the generalizability of our model.

A consistent feature of cancer progression is the deregulation of gene expression and dysfunctional cellular interactions, which dynamically influence tumour cell invasion and metastasis [45, 46]. Numerous oncogenes and tumour suppressors, organized into networks or

pathways, play pivotal roles in cancer progression [47]. Pathway-based approaches and functional experimental studies have been employed to identify the dysfunction of various signaling cascades in NPC recurrence (e.g., the MAPK/RAS, PI3K/AKT/mTOR, WNT signaling, and intrinsic caspase pathways) and disease-related biomarkers [48]. While some biomarkers are effective in predicting and identifying NPC recurrence, pinpointing the critical state or tipping point before recurrence initiation for early diagnosis remains challenging. Recently, the integration of network and dynamics studies has introduced new strategies for addressing the critical transition problem, potentially leading to the development of dynamic biomarkers [18]. In this study, we employed an analysis of biological tipping points based on DNB theory and identified the ER period as the critical phase in NPC malignant progression. Furthermore, we observed that this stage is associated with the negative regulation of the immune response, suggesting that an immunosuppressive state may contribute to early recurrence in NPC. Previous research has demonstrated that the NPC tumor microenvironment can impede antitumor immune responses through immunosuppression [49]. This phenomenon may result from the frequent infiltration of varied stromal cells in NPC, creating a highly heterogeneous and suppressive microenvironment that protects tumor cells from drug penetration and immune attack, thereby facilitating tumor development [50].

Limitations

Our findings underscore the significance of response duration in the progression of NPC. However, several limitations must be acknowledged. First, the retrospective design of this study inherently introduces bias, although we mitigated this through a large sample size. Second, our machine learning model incorporated only tumor-related variables, which limits the model to being more idealistic. Moreover, due to data constraints, our models lacked external validation, these would be considered in future research. Third, the treatment strategies employed for recurrence were not consistently documented, precluding analysis of their direct impact. Lastly, the investigation into the mechanisms of early recurrence remains largely theoretical that the complicated problem of detecting the critical transition during NPC progression has only been challenged by studying tissue sequencing data. Further basic research is necessary to elucidate the biological functions associated with early recurrence and to enhance our understanding of the underlying pathogenetic molecular events in NPC.

Conclusions

In conclusion, our analysis of recurrence characteristics in NPC patients has revealed potential predictive factors for earlier recurrence, which may offer valuable insights for individualized prognostic predictions and the development of targeted surveillance strategies for NPC.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13005-024-00457-7.

Supplementary Material 1

Acknowledgements

The BioTIP is made possible by contributions from the following authors: Yang XH, Wang Z, Goldstein A, Sun Y, Rowton M, Wang Y, Griggs D, Moskowitz I, and Cunningham JM, for which we extend our sincere gratitude.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Huang Z, Zeng X and Wu L. The first draft of the manuscript was written by Li Y and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

This work was supported by the grants of Science and Technology Program of Fujian Province, China (2018Y2003); Fujian Provincial Clinical Research Center for Cancer Radiotherapy and Immunotherapy (2020Y2012); the National Clinical Key Specialty Construction Program (2021); Fujian Clinical Research Center for Radiation and Therapy of Digestive, Respiratory and Genitourinary Malignancies (2021Y2014). National Natural Science Foundation of China (82072986); Major Scientific Research Program for Young and Middle-aged Health Professionals of Fujian Province, China (Grant No.2021ZQNZD010); Science and Technology Pilot Program of Fujian Province, China (2021Y0053); the Qihang Funds of Fujian Medical University (2023QH2050, 2022QH2048); and High-level Talent Training Program of Fujian Cancer Hospital (2022YNG07).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was approved by the appropriate Research Ethics Committee at the Fujian Cancer Hospital (K2022-030-01), with retrospective nature of the study rendering patient informed consent unnecessary

Competing interests

The authors declare no competing interests.

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Received: 30 July 2024 / Accepted: 16 September 2024
Published online: 28 September 2024

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