Establishment of an integrated model for predicting survival and guiding treatment in local recurrence nasopharyngeal carcinoma

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Abstract

Objective:

In this study, we aimed to establish an integrated prognostic model for local recurrence nasopharyngeal carcinoma (lrNPC) patients, and evaluate the benefit of re-radiotherapy (RT) in patients with different risk levels.

Materials and methods:

In total, 271 patients with lrNPC were retrospectively reviewed in this study. Overall survival (OS) was the primary endpoint. Multivariate analysis was performed to select the significant prognostic factors ($P<0.05$). A prognostic model for OS was derived by recursive partitioning analysis (RPA) combining independent predictors using the algorithm of optimized binary partition.

Results:

Three independent prognostic factors (age, relapsed T [rT] stage, and Epstein-Barr virus [EBV] DNA) were identified from multivariable analysis. Five prognostic groups were derived from an RPA model that combined rT stage and EBV DNA. After further pair-wise comparisons of survival outcome in each group, three risk groups were generated. We investigated the role of re-RT in different risk groups, and found that re-RT could benefit patients in the low ($P<0.001$) and intermediate-risk subgroups ($P=0.017$), while no association between re-RT and survival benefit was found in the high-risk subgroup ($P=0.328$).

Conclusion:

Age, rT stage and EBV DNA were identified as independent predictors for lrNPC. We established an integrated RPA-based prognostic model for OS incorporating rT stage and EBV DNA, which could guide individual treatment for lrNPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a malignancy arising from the nasopharyngeal mucosal lining, which is endemic in Southern China with an incidence rate ranging from 20 to 30 per 100,000 individuals [1, 2]. Depending on the stage of the disease, radiotherapy (RT) with or without chemotherapy was the standard treatment method for primary NPC [3, 4]. Nowadays, intensity-modulated radiotherapy (IMRT) is widely applied with the development of RT technology, and excellent local control is achieved as a result [5-7]. Nevertheless, 5% to 10% of NPC patients cannot avoid local recurrence, which remains a challenge in clinical work [8, 9].

There is currently no consensus on the best management of local recurrence NPC (lrNPC). Aggressive treatments such as salvage surgical resection and re-RT brought hope to these patients for achieving long-term survival. Due to a lack of expertise and selection of patients with indications, the application of

surgical resection is limited [10]. High dose re-irradiation was the only treatment method for curing patients with unresectable diseases [11]. However, the radiation toxicity of re-RT was a serious problem and might exceed the survival benefit. Therefore, it was necessary to establish a prognostic model and select the patients who might benefit from additional re-RT.

The invasive range of recurrence lesions based on the rTNM system and Epstein-Barr virus (EBV) DNA status at diagnosis of recurrence were verified to be prognostic factors for lrNPC [12-15]. In this study, we developed a recursive partitioning analysis (RPA)-based prognostic model which combined rT stage and EBV DNA for lrNPC. Through this model, all patients were divided into different risk subgroups. We also assessed the survival rates of patients treated with or without re-irradiation in different risk subgroups, which could provide important information for individual treatment.

Methods And Materials

Patients

From January 2006 to December 2016, 271 lrNPC patients were involved in this study. The inclusion criteria were as follows: (1) rT1-4 N0-1 NPC with pathological diagnosis or imaging evidence; (2) no cervical lymph nodes recurrence and distant metastases; (3) with or without retropharyngeal lymph node metastasis; (4) absence of pregnancy and lactation; (5) no secondary malignancy; (6) adequate renal and liver function; (7) available data of pre-treatment EBV DNA level. All patients involved were restaged according to the 8th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system. The study protocol was approved by the Research Ethics Committee of the Cancer Center of Sun Yat-sen University.

Diagnosis and treatment

A series of evaluations were applied on each patient: physical examination, nasopharyngoscopy, head and neck magnetic resonance imaging (MRI), chest radiography/computed tomography (CT), abdominal sonography/CT, complete blood sampling including differential cell counts, biochemical profile, and plasma EBV DNA. The method of EBV DNA measurement was as in the previous study and the details are supplied in Supplementary Materials [16]. All patients were restaged by at least two radiation oncologists specializing in head and neck cancer.

Platinum-based palliative chemotherapy (PCT) was applied in 202 (74.5%) patients (125 patients in the PCT alone group, and 77 patients in the Re-RT±PCT group). The common chemotherapy regimens were as follows: PF regimen: cisplatin (20–30mg/m2 on d1–3) plus 5-fluorouracil (4–5g/m2, 120 hours continuous IV infusion); TP regimen: docetaxel (70–80mg/m2 d 1) plus cisplatin (20–25mg/m2 d 1–3); TPF regimen: docetaxel (60–70mg/m2 d 1) plus cisplatin (20–25mg/m2 d 1–3) plus 5-fluorouracil (3–3.75g/m2, 120 hours continuous IV infusion); and GP regimen: gemcitabine (0.8–1g/m2 d 1, 8) plus cisplatin (20–30mg/m2 d 1–3). All PCT regimens were administered every three weeks. A total of 146 patients received re-RT. IMRT was the only RT method, which was designed based on the treatment

protocol for lrNPC in our treatment center. The total dose of radiotherapy was 60-70 Gy for recurrent gross tumors and 50–54 Gy for clinical tumor volume in fractions between 25 to 35.

Outcome and follow-up

Overall survival (OS) was the primary endpoint in the current study, defined as the time from the date of lrNPC diagnosis to the date of death from any cause or the date of patients' censoring at the last follow-up. After the completion of treatment, each patient received follow-up examinations every three months in the first three years, and every six months thereafter until death. During the visit, nasopharyngoscopy, head and neck MRI, chest radiography/CT, and abdominal sonography/CT were routinely performed. Patients with a clinical suspicion of distant lesions were recommended for 18F-fluorodeoxy- glucose positron emission tomography (PET)-CT.

Statistical analysis

All the continuous variables were converted to categorical variables determined by recognized or clinical cutoff values. Fisher's exact test and $\chi 2$ test were applied to evaluate the patients' characteristics between different treatment groups. The survival curves were established using Kaplan–Meier method with a log rank test. Univariate and multivariate Cox proportional hazards models were performed on all potential prognosis factors. The backward stepwise approach was used to select the variables in multivariate analysis. Variables that achieved significance at $P < 0.05$ were entered into a RPA model based on the algorithm of optimized binary partition. All the statistical analysis was performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA).

Result

Patient characteristics

In the current study, we retrospectively enrolled 271 lrNPC patients with disease diagnosed from January 2006 to December 2016. Among them, 146 (53.9%) patients received re-RT with or without PCT, while 125 (46.1%) received PCT alone. The median age in the entire cohort was 47 years (range, 22-74 years), and the male:female ratio was 3.7:1. EBV DNA levels could be detected in 154 (56.8%) patients when recurrence occurred. The median follow-up was 20.1 months (interquartile range, 15.3 to 44.6) and a total of 194 of the 271 patients were dead at their last follow-up. The details of patient characteristics are listed in Table 1.

Independent prognosis factors for lrNPC

The results of multivariate analysis are in Table 2. In multivariate analyses, all potential prognostic factors were considered, which included patient age, sex, smoking history, NPC family history, rT stage, rN stage, time intervals (between initial radiation and recurrence) and EBV DNA level. The backward stepwise approach was applied for variables selection. Finally, patient age (>60 vs. ≤60: hazard ratio [HR]: 1.757, 95% confidence interval [CI]: 1.181-2.615, P = 0.005), rT stage (rT2 vs. rT1: HR: 1.725, 95% CI:

0.919-3.241, P = 0.090; rT3 vs. rT1: HR: 2.439, 95% CI: 1.453-4.096, P = 0.001; rT4 vs. rT1: HR: 5.007, 95% CI: 2.989-8.388, P < 0.001) and EBV DNA level (detectable vs. undetectable: HR: 1.825, 95% CI: 1.355-2.459, P < 0.001) remained independent prognosis factors.

RPA-based prognostic model for OS

Based on the independent prognostic factors (age, rT stage and EBV DNA), we developed an integrated prognostic model with the method of RPA. Then, five groups were derived: group A (rT stage 1 + any EBV DNA), group B (rT stage 2-3 + undetectable EBV DNA), group C (rT stage 2-3 + detectable EBV DNA), group D (rT stage 4 + undetectable EBV DNA) and group E (rT stage 4 + detectable EBV DNA) (Figure 1). The Kaplan-Meier curves of each group are shown in Figure 2. Further pair-wise comparisons showed that there was no significant difference in OS between group A and group B, and the same condition was found in group C and group D (Table 3). Therefore, we combined group A and group B as the low-risk group, and combined group C and group D as the intermediate-risk group. In total, 99 (36.5%), 119 (43.9%), and 53 (19.6%) patients were assigned to low, intermediate and high-risk groups, respectively, with corresponding three-year OS rates of 60.9%, 33.3%, and 11.0% (P <0.001 for each of the two groups) (Figure 3).

The role of re-RT in patients according to risk subgroups

We further investigated the treatment value of re-RT in patients with different risk groups. The clinical characteristics in different risk groups were shown in Table 4. Interestingly, the role of re-RT was different in different risk groups. In the low- and intermediate-risk groups, patients treated with re-RT achieved higher three-year OS compared with patients treated with PCT alone (low-risk: 72.8% vs. 42.9%, P = 0.001; intermediate-risk: 37.5% vs. 28.7%, P = 0.017). However, the survival benefit of re-RT for lrNPC was not found in the high-risk group, and the three-year OS rate was similar in these two treatment groups (12.5% vs. 4.8%, P = 0.328) (Figure 4). Then, we conducted three separate multivariate analyses of the low, intermediate and high-risk patients. After adjustment for age, rT stage and EBV DNA level, re-RT was an independent prognostic factor in the low and intermediate-risk groups (low-risk: HR: 0.388; 95% CI: 0.217-0.692; P = 0.001; intermediate-risk: HR: 0.539; 95% CI, 0.357-0.815; P = 0.003). However, re-RT was not associated with better OS in high-risk patients (HR: 0.716; 95% CI: 0.399-1.288; P = 0.265) (Table 5).

Discussion

The current AJCC/UICC TNM showed limited value for relapse patients and a prognostic model needs to be established for predicting survival and guiding treatment. In this study, our group developed the first integrated RPA-based prognostic model for lrNPC incorporated rT stage and EBV DNA. Using this model, all patients could be divided into three risk levels, and we found that the application of re-RT was a protective factor in the low and intermediate-risk subgroups.

Radical RT was the standard treatment for primary NPC [17]. However, it needs careful consideration before the application of a second course of RT for locally recurrent NPC as it has severe complications

[18-20]. Thus, the management of locally recurrent NPC remained a crucial clinical challenge [21, 22]. The development of the RT technique, IMRT, which had a precise dose distribution to the tumor area and adjacent normal tissue, meant that this was applied more often in the treatment of NPC [5-7]. Unfortunately, radiation toxicity was still a serious problem even in patients with rT1-2 stage [23]. As mentioned above, it is important to identify the candidates who may benefit from re-RT.

Previous studies investigated the efficacy and toxicity of re-RT in lrNPC in the IMRT era. Qiu et al. reported the survival outcome of a cohort with 70 lrNPC patients receiving re-irradiation with IMRT and concluded that re-RT provides reasonable long-term control [24]. Notably, treatment was interrupted in five patients because of serious adverse effects. Contrary to the above viewpoints, Hua et al. demonstrated that only patients with early re-stage diseases achieved satisfactory clinical outcomes under re-RT, while higher incidences of Grade 3 or 4 toxicities might eliminate the survival benefit of re-RT in patients (39.0%) with re-stage III or IV disease [25]. Tian et al. gave a similar opinion that re-irradiation with IMRT was an effective strategy in the management of advanced lrNPC [12]. However, severe late complications offset the survival benefits.

Up to now, only a few studies have evaluated the survival outcome of lrNPC treated with or without re-RT. Our group launched the first case-control study to compare the survival of rT3-4 lrNPC patients treated with reirradiation or PCT alone and found that patients in these two groups achieved similar OS [26]. However, You et al. established a new surgical system and verified that a combination of aggressive re-irradiation could further enhance OS compared with PCT alone [27]. Notably, all the studies mentioned above only considered the anatomical extent of recurrent lesions. It was confirmed that some non-anatomic prognostic factors, such as EBV DNA, had a close relationship with the clinical outcome of lrNPC patients [15, 28]. Therefore, a method combining anatomic prognostic factors and biomarkers should be developed for survival prediction and treatment guidance.

In the current study, we integrated an RPA-based prognostic model with rT stage and EBV DNA for predicting survival condition. All patients were divided into five groups: group A (rT stage 1 + any EBV DNA), group B (rT stage 2-3 + undetectable EBV DNA), group C (rT stage 2-3 + detectable EBV DNA), group D (rT stage 4 + undetectable EBV DNA) and group E (rT stage 4 + detectable EBV DNA). After performing pair-wise survival comparisons, three risk groups were generated. We further analyzed the role of re-RT in different risk subgroups. Interestingly, only patients in the low and intermediate-risk subgroups could benefit from aggressive re-RT, while patients in the high-risk subgroup achieved similar OS rates when they received different treatment methods. Our results indicated that re-irradiation was difficult to use to control disease progression in patients suffering huge tumor burdens. Besides, the treatment-related toxicity of re-RT might be another key factor, which was more serious in high-risk patients and eliminated its survival benefit.

Our model meets the needs of clinician for the management of lrNPC. Through this model, patients could be identified into different risk groups, which provides the basis for making the best clinical choice. However, there were also some limitations in our study. First, selection bias was inevitable because of the

nature of the retrospective study. Second, all patients involved in this study were from one treatment center in an endemic area; an external cohort is necessary to validate our results.

Abbreviations

NPC = nasopharyngeal carcinoma; RT = radiotherapy; IMRT = intensity-modulated radiotherapy; lrNPC = local recurrence nasopharyngeal carcinoma; EBV = Epstein-Barr virus; RPA = recursive partitioning analysis; UICC/AJCC = International Union against Cancer/American Joint Committee on Cancer; MRI = magnetic resonance imaging; CT = computed tomography; PCT = palliative chemotherapy; OS = overall survival; PET = positron emission tomography; HR = hazard ratio; CI = confidence interval.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective study was approved by the Clinical Research Committee of Sun Yat Sen University Cancer Center. Patients were required to provide written informed consent before enrolling in the study.

Competing interests

The authors declare no competing interests.

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Tables

Table 1: Patient characteristics and univariate analysis

Characteristic	Number of patients (%)	Univariate analysis	
		Hazard ratio (95% CI)	*P value*
Age (years)	271		
18-60	236 (87.1)	Reference	
>60	35 (12.9)	1.777 (1.202-2.628)	0.004
Gender			
Female	58 (21.4)	Reference	
Male	213 (78.6)	1.563 (1.083-2.255)	0.017
BMI			
<23.5	162 (59.8)	Reference	
≥23.5	109 (40.2)	1.242 (0.935-1.651)	0.135
Smoking history			
No	135 (49.8)	Reference	
Yes	136 (50.2)	1.298 (0.978-1.722)	0.071
NPC family history			
No	236 (87.1)	Reference	
Yes	35 (12.9)	0.729 (0.463-1.147)	0.172
rT stage*			
rT1	45 (16.6)	Reference	
rT2	33 (12.2)	1.822 (0.970-3.420)	0.062
rT3	99 (36.5)	2.518 (1.502-4.223)	<0.001
rT4	94 (34.7)	5.003 (2.993-8.363)	<0.001
rN stage*			
rN0	199 (73.4)	Reference	
rN1	72 (26.6)	1.244 (0.910-1.701)	0.170
TI (months)			
≤36 months	189 (69.7)	Reference	
>36 months	82 (30.3)	1.096 (0.805-1.492)	0.559
EBV DNA level			

Undetectable	117 (43.2)	Reference	
Detectable	154 (56.8)	1.720 (1.281-2.308)	<0.001

Abbreviations: CI = confidence interval; PCT = palliative chemotherapy; Re-RT = Re-radiotherapy; TI = time interval between initial radiation and recurrence; EBV= Epstein-Barr virus

*According to the 8th edition of UICC/AJCC staging system

Table 2: Multivariate analysis

Characteristic	Hazard ratio (95% CI)	*P value*
Age, y		
18-60	Reference	
>60	1.757 (1.181-2.615)	0.005
rT stage*		
rT1	Reference	
rT2	1.725 (0.919-3.241)	0.090
rT3	2.439 (1.453-4.096)	0.001
rT4	5.007 (2.989-8.388)	<0.001
EBV DNA level		
Undetectable	Reference	
Detectable	1.825 (1.355-2.459)	<0.001

Abbreviations: CI = confidence interval; EBV DNA = Epstein-Barr virus DNA;

A Cox proportional hazards model was used to perform multivariate analyses.

We selected variables using a backward stepwise approach. The *P* value threshold was 0.1 (P > 0.1) for removing non-significant variables from the model.

*According to the 8th edition of UICC/AJCC staging system

Table 3. Inter connections between each of the 5 groups.

	X2 Value	Group A	Group B	Group C	Group D	Group E
P value						
Group A			3.482	18.418	23.937	56.590
Group B		0.062		5.358	9.666	31.129
Group C		<0.001	0.021		1.616	19.937
Group D		<0.001	0.002	0.204		4.807
Group E		<0.001	<0.001	<0.001	0.028	

Table 4: Clinical characteristics grouped by treatment methods in different risk groups

	Low risk n(%)			Intermediate risk n(%)			High risk n(%)		
Characteristic	PCT along	Re-RT± PCT	P value	PCT	Re-RT± PCT	P value	PCT along	Re-RT± PCT	P value
Total	40	59		56	63		29	24	
Age, y									
18-60	36 (90.0)	53 (89.8)	1.000	51 (91.1)	54 (85.7)	0.407	22 (75.9)	20 (83.3)	0.735
>60	4 (10.0)	6 (10.2)		5 (8.9)	9 (14.3)		7 (24.1)	4 (16.7)	
Gender									
Female	8 (20.0)	16 (27.1)	0.480	16 (28.6)	12 (19.0)	0.280	4 (13.8)	2 (8.3)	0.678#
Male	32 (80.0)	43 (72.9)		40 (71.4)	51 (81.0)		25 (86.2)	22 (91.7)	
BMI									
<23.5	26 (65.0)	43 (72.9)	0.505	34 (60.7)	31 (49.2)	0.269	19 (65.5)	9 (37.5)	0.056
≥23.5	14 (35.0)	16 (27.1)		22 (39.3)	32 (50.8)		10 (34.5)	15 (62.5)	
Smoking history									
No	23 (57.5)	34 (57.6)	1.000	30 (53.6)	28 (44.4)	0.361	12 (41.4)	8 (33.3)	0.582
Yes	17 (42.5)	25 (42.4)		26 (46.4)	35 (55.6)		17 (58.6)	16 (66.7)	
NPC family history									
No	35 (87.5)	47 (79.7)	0.418	49 (87.5)	56 (88.9)	1.000	27 (93.1)	22 (91.7)	1.000#
Yes	5 (12.5)	12 (20.3)		7 (12.5)	7 (11.1)		2 (6.9)	2 (8.3)	
rT stage*									
rT1	20 (50.0)	25 (42.4)	0.700	–	–	0.197	–	–	–
rT2	5	10		12	6		–	–	

	(12.5)	(16.9)		(21.4)	(9.5)				
rT3	15 (37.5)	24 (40.7)		27 (48.2)	33 (52.4)		--	--	
rT4	--	--		17 (30.4)	24 (38.1)		29 (100.0)	24 (100.0)	
rN stage*									
rN0	30 (75.0)	48 (81.4)	0.464	37 (66.1)	46 (73.0)	0.431	20 (69.0)	18 (75.0)	0.762
rN1	10 (25.0)	11 (18.6)		19 (33.9)	17 (27.0)		9 (31.0)	6 (25.0)	
TI (months)									
≤36 months	32 (80.0)	41 (69.5)	0.258	40 (71.4)	42 (66.7)	0.692	18 (62.1)	16 (66.7)	0.780
>36 months	8 (20.0)	18 (30.5)		16 (28.6)	21 (33.3)		11 (37.9)	8 (33.3)	
EBV DNA level									
Undetectable	27 (67.5)	49 (83.1)	0.091	17 (30.4)	24 (38.1)	0.441	--	--	--
Detectable	13 (32.5)	10 (16.9)		39 (69.6)	39 (61.9)		29 (100.0)	24 (100.0)	

Abbreviations: CI = confidence interval; PCT = palliative chemotherapy; Re-RT = Re-radiotherapy; TI = time interval between initial radiation and recurrence; EBV= Epstein-Barr virus

*According to the 8th edition of UICC/AJCC staging system

P-value was calculated with the Pearson $\chi 2$ test or Fisher's exact test (#)

Table 5: Multivariable analysis for overall survival by treatment modality in stratified risk groups.

	Multivariable analyses		
Treatment method	Adjusted HR	95%CI	*P value*
Re-RT (Yes vs. No)			
Low risk	0.388	0.217-0.692	*0.001*
Intermediate risk	0.539	0.357-0.815	*0.003*
High risk	0.716	0.399-1.288	*0.265*

Abbreviations: HR = ratio; CI = confidence interval; EBV DNA = Epstein-Barr virus DNA;

A Cox proportional hazards model was used to perform multivariate analyses.

Multivariable cox regression model adjusted for age, rT stage, EBV DNA and treatment method.

Figures

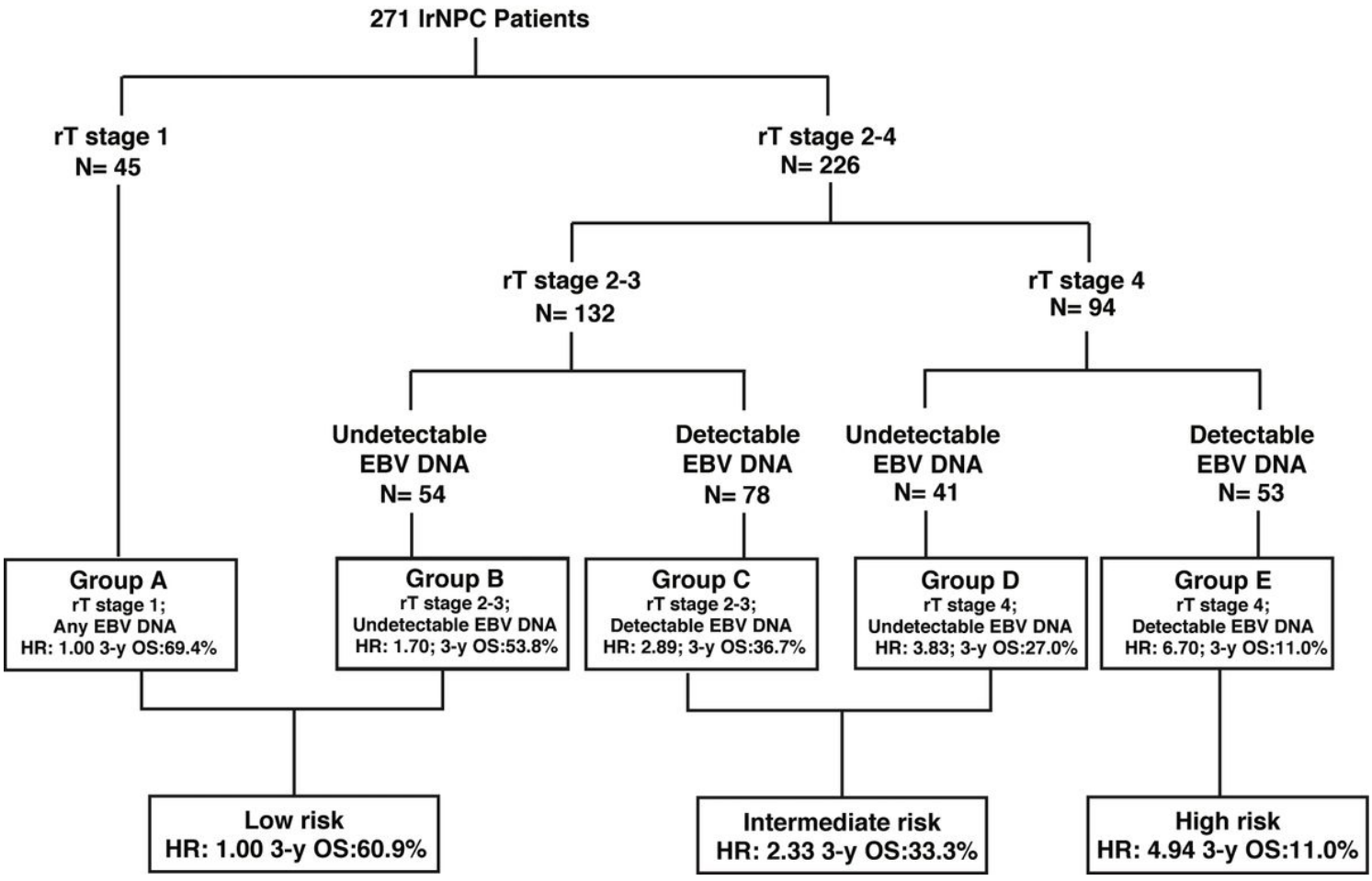

Figure 1

Prognostic model for overall survival using recursive partitioning analysis.

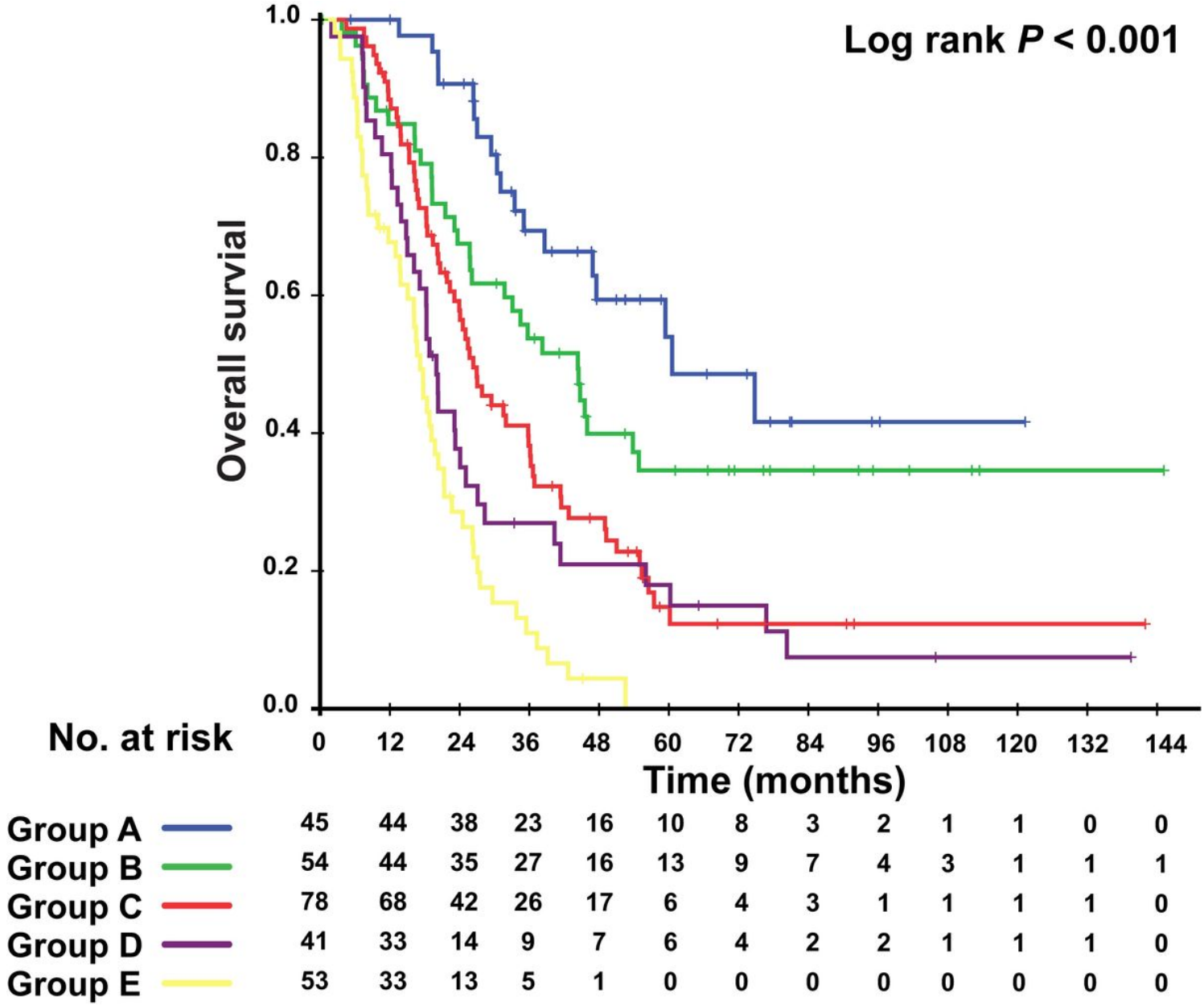

Figure 2

Kaplan-Meier overall survival curves in 271 patients in each derived prognostic group.

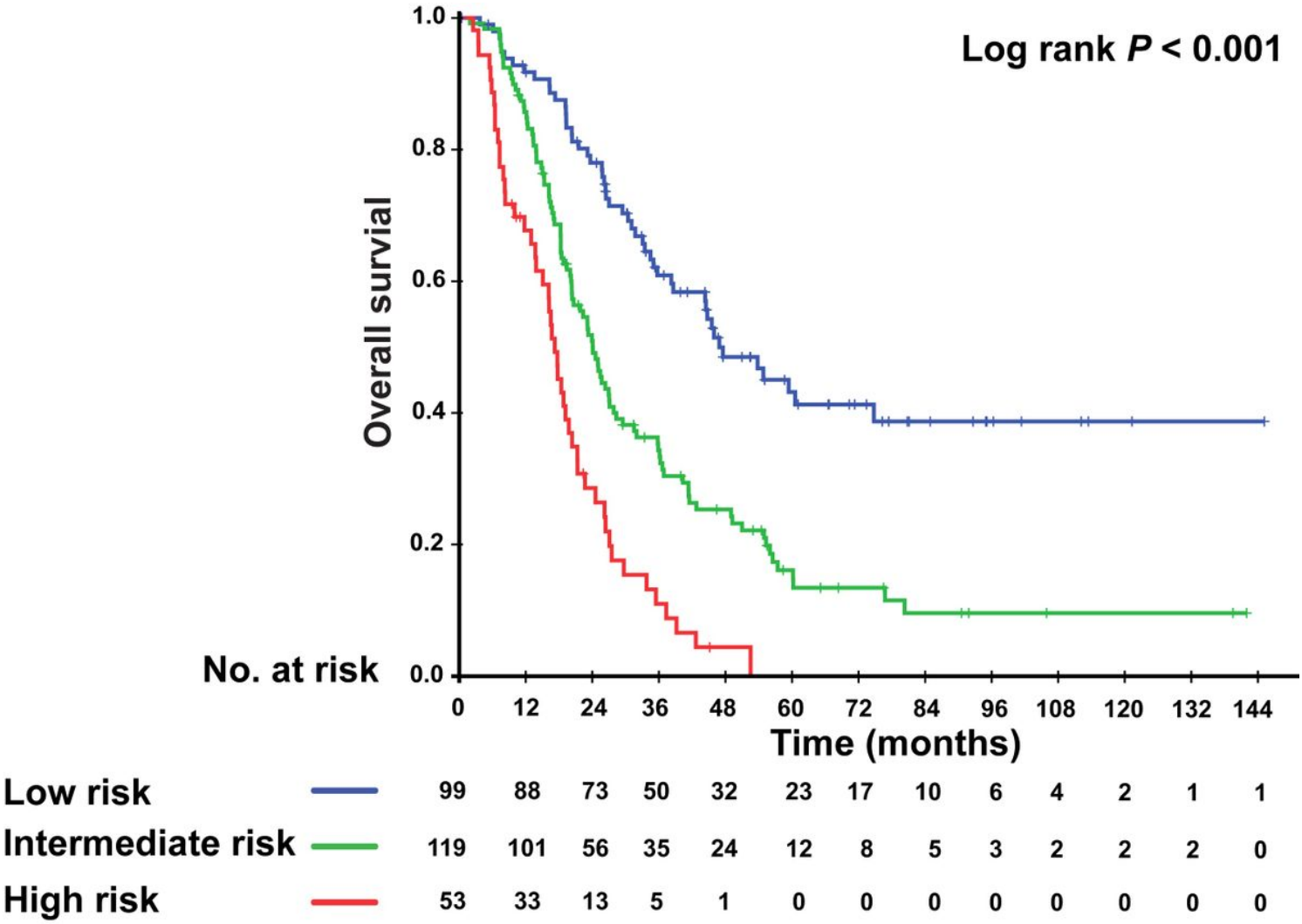

Figure 3

Kaplan-Meier overall survival curves in 271 patients grouped by different risk stratification.

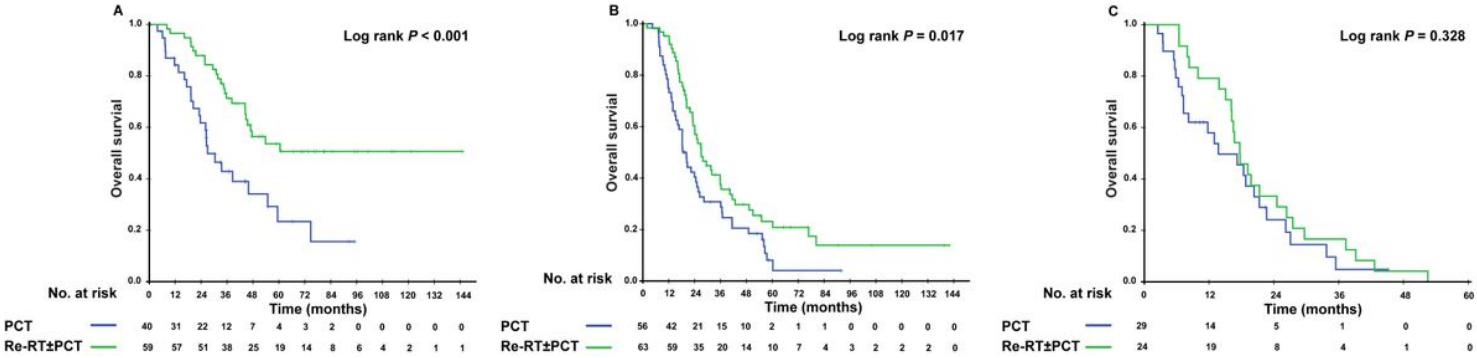

Figure 4

Comparison of overall survival between patients in palliative chemotherapy and re-radiotherapy (re-RT) groups: (A) low-risk patients, (B) intermediate-risk patients, and (C) high-risk patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterials.docx