Mortality of early treatment for radiation-induced brain necrosis in head and neck cancer survivors: a multicentre, retrospective, registry-based cohort study

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Supplementary material

eText: Supplementary statistical methods.

We hypothesized that early medical treatment would reduce the risk of all-cause death for patients with RN. Since we had observed that about two-thirds of patients would receive early treatment in real-world clinical practice, in order to achieve 80% power to detect hazard ratio for the primary outcome of 0.80 using a log-rank test with a two-sided significance level of 0.05, we estimated that 706 patients in a 2:1 ratio (471 patients in the early treatment group, 235 patients in the watch-and-wait group) would be needed. Furthermore, we assumed approximately 20% of patients might need to be excluded in accordance with our inclusion criteria or for lack of follow-up information. Thus, we assumed that at least 848 patients would be needed to be screened. Sample size calculations were performed using PASS software (Version 15.0, NCSS LLC., Kaysville, U.T., USA).

In the primary analysis, “survival” and “survminer” packages were used to perform Cox proportional hazards regression analyses by calling the coxph() function, and to construct the Kaplan-Meier curve and multivariable-adjusted survival curve by calling survfit(), ggsurvplot() and ggadjustedcurves() functions. Since we had performed multiple imputations to handle missing values, the with() function in the "MICE" package was useful for simplifying calls to the model function. Lastly, we pooled the results of 20 imputed datasets in the main analysis, by calling the pool() function. All relevant variables have been used to estimate missing values, including demographic features, medical history, and laboratory results as well as outcomes.

In the propensity-score analyses, the pscore() function in the “nonrandom” package was used to estimate the individual propensity score using a logistic regression model, and ps.match() function was used to create a 1:1 matched dataset, in which treated and controlled observations had similar propensity score, with “nearest-neighbor method” and a 0.05 caliper size (i.e., the maximum distance of propensity

score between treated and controlled observations). The calculation of stabilized weights in the early treatment group: Wt=Pt/ps; in the watch-and-wait group: Wo=(1-Pt)/(1-ps); “Pt” was the proportion of patients receiving early treatment, and “ps” was the individual propensity score.

In the secondary analysis, we used cuminc() and crr() functions in “cmprsk” package to construct univariable and multivariable competing risk regression models, respectively. All statistical tests were two-tailed, and p-values <0.05 were considered significant.

All statistical analyses were performed using R software (Version 4.0.3, R Core Team) for MacOS.

Table S1. Baseline characteristics of 229 patients excluded from the primary analysis.

Characteristics	Ineligible patients	Eligible patients
n	229	641
Sex – no. (%)		
Females	53 (23.1%)	167 (26.1%)
Males	176 (76.9%)	474 (73.9%)
Age – years, median (IQR)	51.6 (44.3-59.1)	51.2 (44.6-58.3)
Symptomatic at diagnosis – no. (%)	162 (70.7%)	400 (62.4%)
Co-existing disorders – no. (%)		
Hypertension	32 (14.0%)	83 (12.9%)
Ischemic or hemorrhagic stroke	3 (1.3%)	38 (5.9%)
Diabetes	8 (3.5%)	25 (3.9%)
Cigarette smoking	33 (14.4%)	81 (12.6%)
Alcohol consumption	20 (8.7%)	35 (5.5%)
Radiotherapy features		
Time from the commencement of RT to diagnosis of RN – years, median (IQR)	4.8 (3.5-7.9); *n*=138	3.7 (2.6-6.4); *n*=432
TNM stage – no. (%)		
I	2/131 (1.5%)	7/432 (1.6%)
II	24/131 (18.3%)	47/432 (10.9%)
III	47/131 (35.9%)	208/432 (48.1%)
IV	58/131 (44.3%)	170/432 (39.4%)
RT techniques – with iMRT, no. (%)	55 (40.1%); *n*=137	193 (44.7%); *n*=432
Nose dose-Gy, mean (SD)	67.7 (12.3); *n*=134	69.7 (6.3); *n*=431
Neck dose-Gy, mean (SD)	53.8 (21.3); *n*=134	57.7 (17.3); *n*=431
Received chemotherapy – no. (%)	94 (68.1%); *n*=138	339 (78.5%); *n*=432
Brain MRI findings – no. (%)		
Bilateral lesions	108 (47.2%)	377 (58.8%)
Involving ≥ 2 brain regions	62 (27.1%)	89 (13.9%)
With brain stem lesions	4 (1.8%)	20 (3.1%)
All-cause death – no. (%)	73 (31.9%)	112 (17.5%)
Causes-specific death – no. (%)		
Cancer-specific death	24 (10.5%)	40 (6.2%)
RT complications-related death	24 (10.5%)	43 (6.7%)
Others	25 (10.9%)	29 (4.5%)

Abbreviations: no., Numbers; SD, Standard Deviation; IQR, Interquartile Range; RN, Radiation-induced brain necrosis; RT, Radiotherapy; iMRT, Intensity-modulated radiation therapy; MRI, Magnetic resonance imaging.

Table S2. The Cox model for estimating the effect of early treatment on the primary outcome.

	Estimates	Std. Error	p values
Early treatment (studied exposure)	-0.728	0.235	0.0027
Sex (male)	0.381	0.262	0.15
Age (years)	0.044	0.011	0.00027
Symptomatic at diagnosis	-0.126	0.218	0.56
History of stroke	0.241	0.397	0.55
Bilateral lesions	0.717	0.239	0.0035
Lesions involving ≥2 brain regions	0.505	0.270	0.065
With brain stem lesions	0.573	0.541	0.30
RT technique (iMRT)	-0.468	0.315	0.14
Time from RT to RN (years)	0.013	0.042	0.76
Having Received chemotherapy	-0.261	0.372	0.49
Nose RT dose (Gy)	-0.008	0.018	0.65
Neck RT dose (Gy)	-0.008	0.012	0.52
TNM stage			
I (Reference)	..	..	..
II	0.726	0.651	0.28
III	0.848	0.662	0.21
IV	1.188	0.688	0.097

Table S3. Multivariable Cox regression analyses performed in each imputed dataset.

	Dataset 1	**Dataset 2**	**Dataset 3**	**Dataset 4**	**Dataset 5**
Hazard ratios	0.48	0.53	0.42	0.52	0.45
95% CIs	0.31-0.74	0.34-0.82	0.26-0.66	0.34-0.82	0.29-0.71
p values	0.00090	0.0050	0.00018	0.0041	0.00050
	Dataset 6	**Dataset 7**	**Dataset 8**	**Dataset 9**	**Dataset 10**
Hazard ratios	0.48	0.45	0.49	0.45	0.48
95% CIs	0.31-0.75	0.29-0.70	0.31-0.75	0.29-0.70	0.31-0.74
p values	0.0010	0.00039	0.0013	0.00039	0.00099
	Dataset 11	**Dataset 12**	**Dataset 13**	**Dataset 14**	**Dataset 15**
Hazard ratios	0.49	0.49	0.51	0.46	0.51
95% CIs	0.31-0.77	0.31-0.77	0.32-0.81	0.29-0.72	0.33-0.78
p values	0.0019	0.0019	0.0039	0.00062	0.0022
	Dataset 16	**Dataset 17**	**Dataset 18**	**Dataset 19**	**Dataset 20**
Hazard ratios	0.49	0.53	0.47	0.51	0.47
95% CIs	0.32-0.77	0.34-0.83	0.30-0.74	0.33-0.79	0.30-0.74
p values	0.0017	0.0054	0.00090	0.0022	0.0010
	Pooled results				
Hazard ratios	0.48				
95% CIs	0.30-0.77				
p values	0.0027				

Table S4. The logistic regression model for the estimates of individual propensities for receiving early treatment in the first imputed dataset.

	Estimates	Std. Error	p values
(Intercept)	1.720	0.686	0.012
Sex (male)	-0.244	0.213	0.25
Age (years)	-0.030	0.009	0.0012
Symptomatic at diagnosis	0.052	0.189	0.78
History of stroke	-0.383	0.357	0.28
Bilateral lesions	0.326	0.194	0.092
Lesions involving ≥2 brain regions	0.451	0.312	0.149
With brain stem lesions	0.303	0.629	0.63
RT technique (iMRT)	-0.492	0.210	0.019
Time from RT to RN (years)	-0.039	0.017	0.023
Having Received chemotherapy	0.078	0.228	0.73
Nose RT dose (Gy)	0.007	0.006	0.26
Neck RT dose (Gy)	0.006	0.004	0.12
TNM stage			
I (Reference)	..	..	..
II	0.745	0.440	0.090
III	0.355	0.387	0.36
IV	0.127	0.398	0.75

Table S5. The standardized mean differences before and after stabilized IPTW based on propensity-score in the first imputed dataset.

Covariates	SMD before IPTW	SMD after IPTW
Sex (male)	0.060	0.003
Age (years)	0.292	0.013
Symptomatic at diagnosis	0.055	0.054
History of stroke	0.171	0.012
Bilateral lesions	0.239	0.022
Lesions involving ≥2 brain regions	0.190	0.034
With brain stem lesions	0.087	0.015
RT technique (iMRT)	0.263	0.045
Time from RT to RN (years)	0.135	0.019
Having Received chemotherapy	0.012	0.019
Nose RT dose (Gy)	0.119	0.033
Neck RT dose (Gy)	0.161	0.037
TNM stage	0.182	0.022

Table S6. The standardized mean differences before and after 1:1 propensity-score matching in the first imputed dataset.

Covariates	SMD before PSM	SMD after PSM
Sex (male)	0.059	0.065
Age (years)	0.317	0.040
Symptomatic at diagnosis	0.055	0.036
History of stroke	0.204	0.027
Bilateral lesions	0.241	0.119
Lesions involving ≥2 brain regions	0.172	0.016
With brain stem lesions	0.078	0.000
RT technique (iMRT)	0.266	0.035
Time from RT to RN (years)	0.163	0.083
Having Received chemotherapy	0.012	0.048
Nose RT dose (Gy)	0.127	0.053
Neck RT dose (Gy)	0.172	0.082
TNM stage	0.114	0.050

Table S7. Hazard ratios and their 95% CIs from propensity-score analyses in each imputed dataset.

	Dataset 1	**Dataset 2**	**Dataset 3**	**Dataset 4**	**Dataset 5**
Stabilized IPTW	0.52 (0.35-0.79)	0.62 (0.40-0.94)	0.55 (0.36-0.84)	0.56 (0.37-0.85)	0.52 (0.34-0.79)
1:1 matching	0.46 (0.25-0.83)	0.51 (0.29-0.90)	0.38 (0.21-0.69)	0.57 (0.33-0.995)	0.44 (0.25-0.77)
Additional adjustment for propensity score	0.48 (0.31-0.74)	0.53 (0.34-0.83)	0.41 (0.26-0.65)	0.52 (0.34-0.82)	0.45 (0.29-0.71)
	Dataset 6	**Dataset 7**	**Dataset 8**	**Dataset 9**	**Dataset 10**
Stabilized IPTW	0.52 (0.34-0.78)	0.51 (0.33-0.77)	0.54 (0.35-0.81)	0.54 (0.35-0.82)	0.48 (0.32-0.74)
1:1 matching	0.50 (0.29-0.85)	0.44 (0.25-0.78)	0.73 (0.44-1.23)	0.36 (0.18-0.66)	0.64 (0.37-1.11)
Additional adjustment for propensity score	0.48 (0.31-0.75)	0.45 (0.29-0.70)	0.48 (0.31-0.75)	0.45 (0.29-0.70)	0.48 (0.31-0.75)
	Dataset 11	**Dataset 12**	**Dataset 13**	**Dataset 14**	**Dataset 15**
Stabilized IPTW	0.52 (0.34-0.80)	0.49 (0.32-0.74)	0.55 (0.36-0.83)	0.49 (0.32-0.75)	0.51 (0.34-0.78)
1:1 matching	0.45 (0.26-0.79)	0.46 (0.26-0.82)	0.50 (0.27-0.91)	0.51 (0.28-0.90)	0.46 (0.26-0.83)
Additional adjustment for propensity score	0.49 (0.31-0.77)	0.49 (0.31-0.77)	0.51 (0.32-0.80)	0.46 (0.29-0.72)	0.50 (0.32-0.78)
	Dataset 16	**Dataset 17**	**Dataset 18**	**Dataset 19**	**Dataset 20**
Stabilized IPTW	0.47 (0.31-0.72)	0.50 (0.33-0.76)	0.51 (0.34-0.77)	0.55 (0.36-0.83)	0.47 (0.31-0.73)
1:1 matching	0.50 (0.28-0.90)	0.55 (0.33-0.93)	0.48 (0.28-0.82)	0.69 (0.39-1.22)	0.55 (0.32-0.94)
Additional adjustment for propensity score	0.49 (0.32-0.77)	0.53 (0.34-0.83)	0.47 (0.30-0.73)	0.51 (0.33-0.78)	0.47 (0.30-0.74)

Figure S1. The unadjusted Kaplan-Meier curve for post-RN survival.

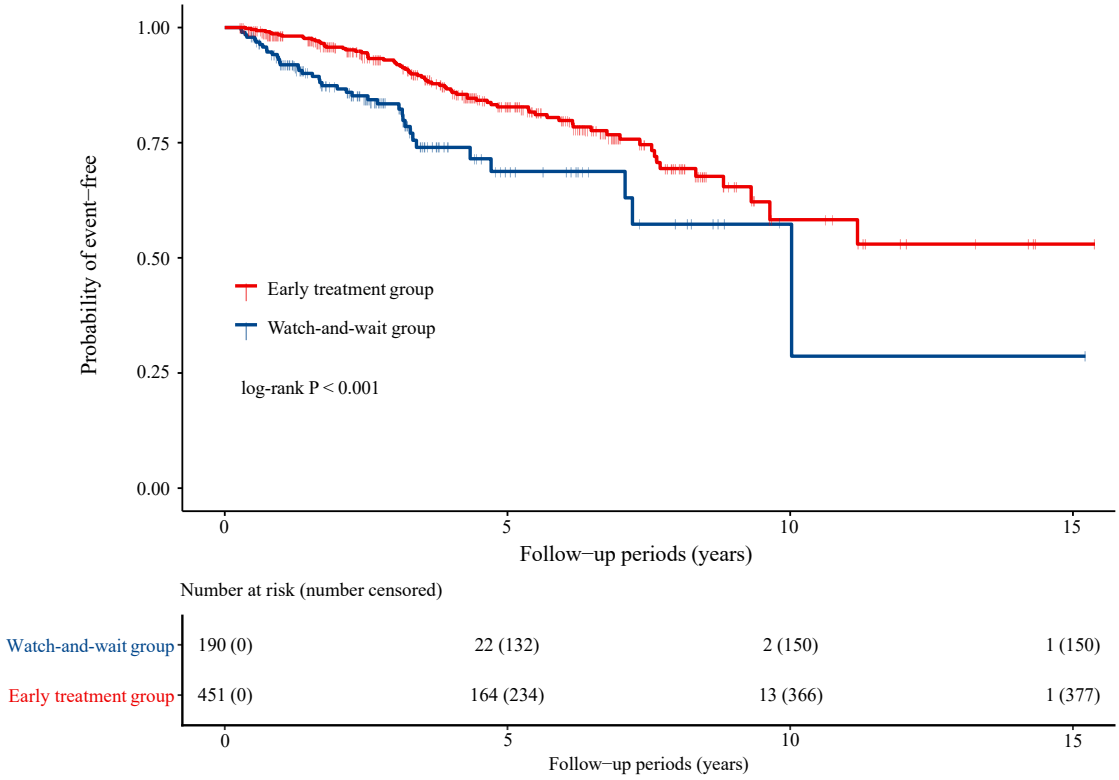
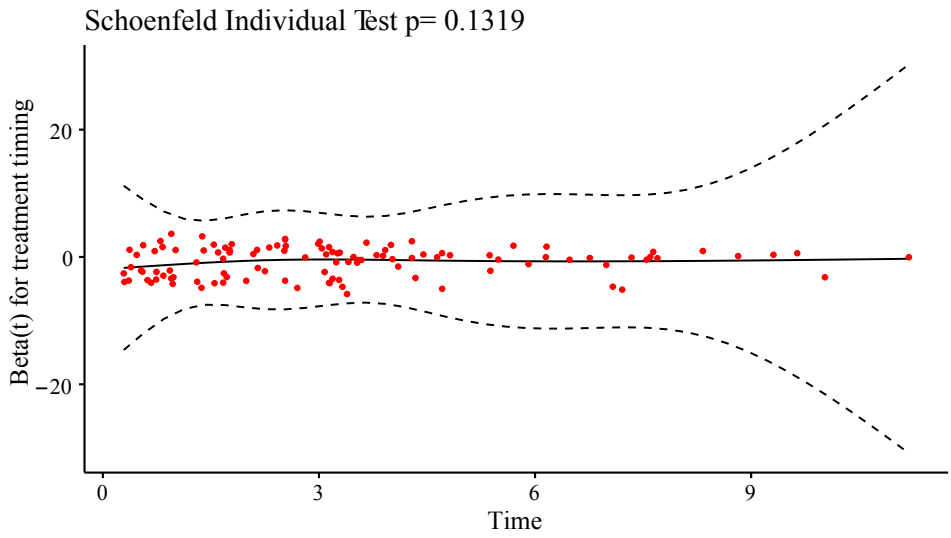
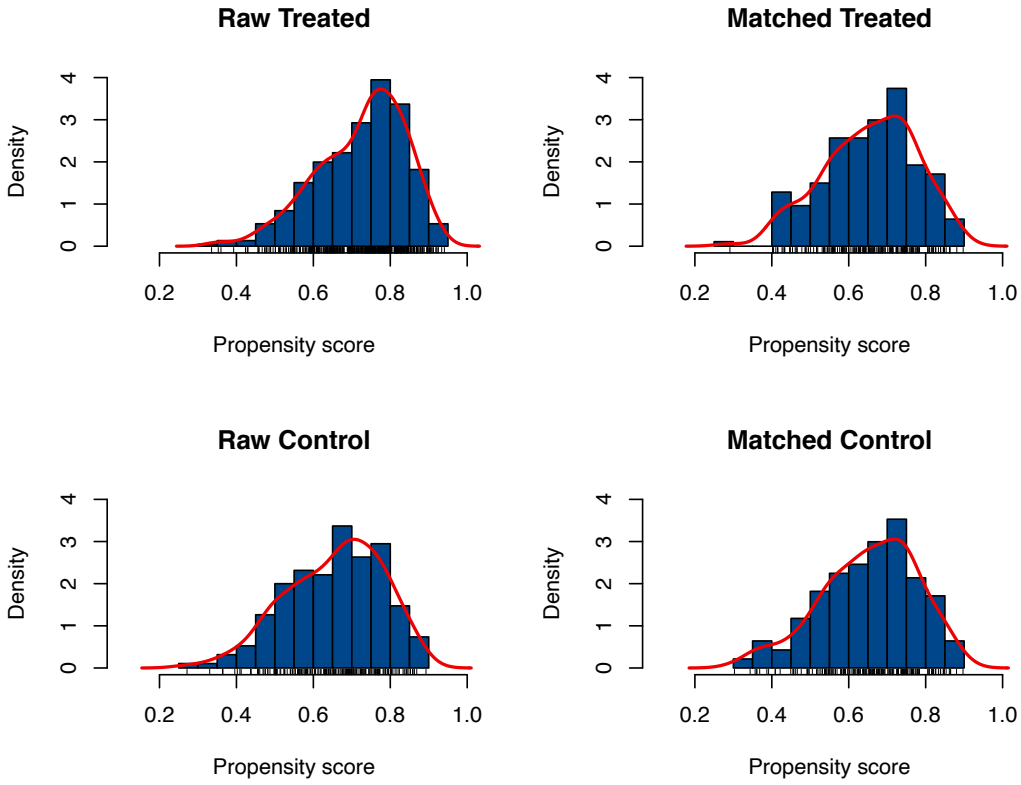


Figure S2. The plot of Schoenfeld residuals.



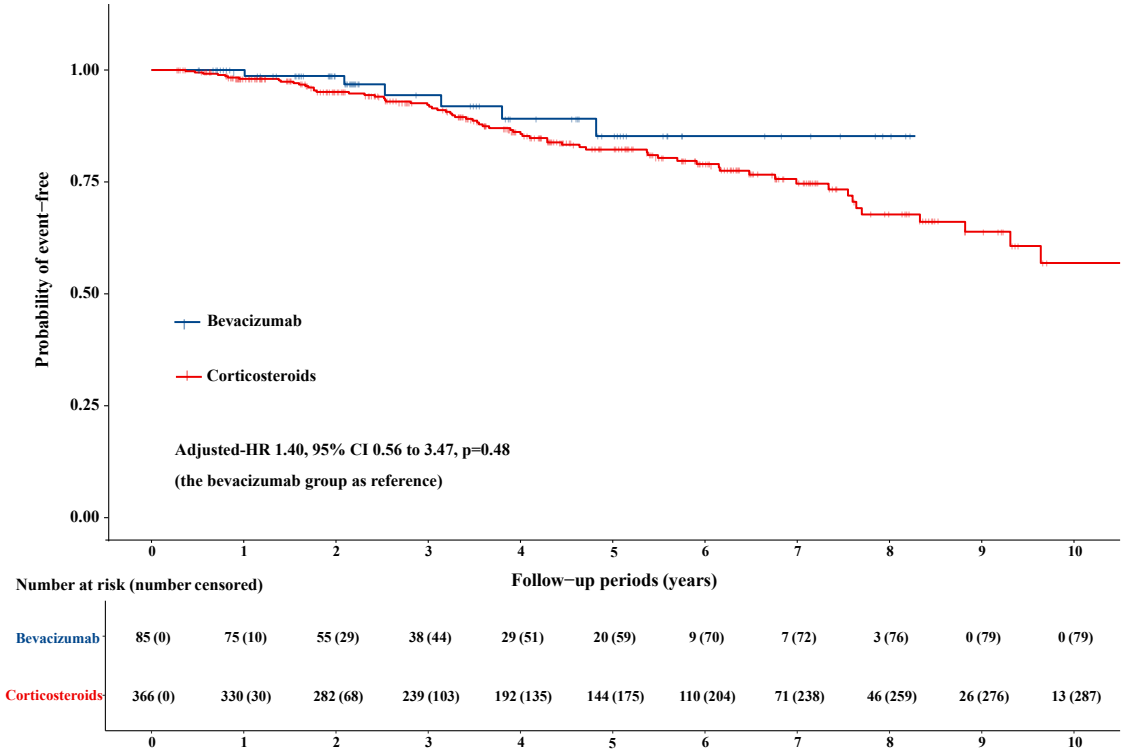
The proportional hazard assumption was not violated, as the hazard ratio did not change over time.

Figure S3. The propensity-score distribution before and after matching in the first imputed database.



Treated=early treatment group; Control=watch-and-wait group.

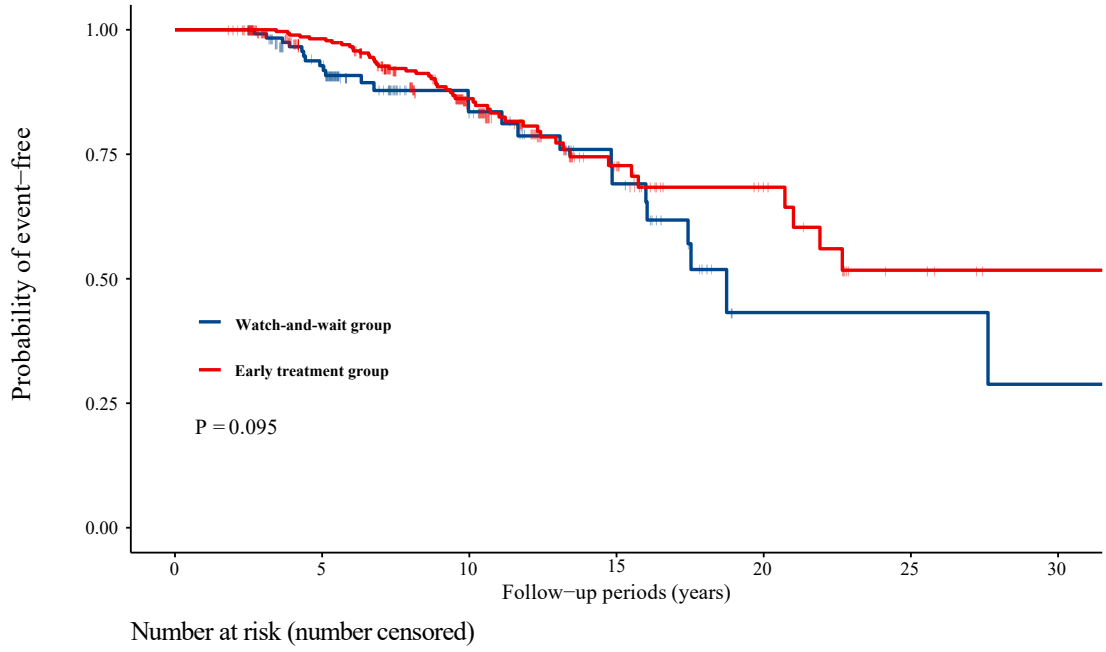
Figure S4. The comparison of bevacizumab vs corticosteroids on post-RN survival.



Number at risk (number censored)

	0	1	2	3	4	5	6	7	8	9	10
Bevacizumab	85 (0)	75 (10)	55 (29)	38 (44)	29 (51)	20 (59)	9 (70)	7 (72)	3 (76)	0 (79)	0 (79)
Corticosteroids	366 (0)	330 (30)	282 (68)	239 (103)	192 (135)	144 (175)	110 (204)	71 (238)	46 (259)	26 (276)	13 (287)

Figure S5. Exploratory analysis of overall survival from the commencement of RT.



Number at risk (number censored)

Watch-and-wait	121 (0)	96 (17)	39 (68)	20 (82)	3 (94)	3 (94)	2 (94)
Early treatment	311 (0)	256 (50)	131 (150)	40 (230)	20 (246)	6 (256)	2 (260)

The KM curve displayed below is a sensitivity analysis, in which we only included the sample that there was no missing data (432 patients) and the study baseline was set to the commencement of RT.

The log-rank test showed no statistical significance on mortality of different timing of treatment (log-rank p=0.095), while multivariable Cox regression analysis showed that the point estimate of hazard ratio on all-cause mortality were **0.38 (95%CI, 0.21-0.69; p=0.001)** after adjusting for confounders (as the same covariates in the main analysis), which still favored the choice of early treatment for RN.