

Clinicopathological Factors and Prognosis of Massive Hemorrhage After Radiotherapy for Nasopharyngeal Carcinoma

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Abstract

Background: To investigate the clinicopathological factors and prognosis of nasopharyngeal hemorrhage after radiotherapy for nasopharyngeal carcinoma (NPC).

Methods: The clinicopathological data of 539 NPC patients who received radiotherapy were analyzed retrospectively, including gender; age; T-stage; N-stage; pathological type; type of radiotherapy; synchronous chemotherapy; secondary-course radiotherapy; radioactive skull base osteonecrosis; diabetes, hypertension, or other systemic diseases; results of nasopharyngeal bacterial culture. Univariate and multivariate analyses were performed using the χ^2 test and logistic regression. The Kaplan-Meier method was applied to analyze the survival of patients with nasopharyngeal hemorrhage.

Results: Among all patients, 64 (11.9%) had nasopharyngeal hemorrhage after radiotherapy. Results from the univariate analysis showed that T-stage ($p<0.01$), secondary-course radiotherapy ($p<0.01$), radioactive skull base osteonecrosis ($p<0.01$), nasopharyngeal bacterial culture results ($p<0.01$), and nasopharyngeal tumor recurrence ($p<0.01$) were associated with nasopharyngeal hemorrhage. Multivariate analysis showed that only radioactive skull base osteonecrosis was significantly associated with nasopharyngeal hemorrhage after radiotherapy (OR=41.83, $p=0.0001$). In patients with internal carotid artery hemorrhage, the survival rate was 60.9% in one year, 15.1% in 3 years, and 0% in 5 years. In patients with external carotid artery bleeding, the 5-year survival rate was 50%. The main cause of death during follow-up was rebleeding.

Conclusion: The rate of mortality in patients with nasopharyngeal hemorrhage after radiotherapy is high. The presence of radioactive skull base osteonecrosis is the decisive factor in patients with nasopharyngeal hemorrhage after radiotherapy. Influencing and synergistic factors include T-stage, secondary-course radiotherapy, results of nasopharyngeal bacterial culture, and nasopharyngeal tumor recurrence. After successful rescue, arterial embolization or stent implantation may prolong survival.

Background

Nasopharyngeal carcinoma (NPC) is one of the most common head and neck malignancies in South China. Recent epidemiological data have shown that the incidence of NPC varies across regions, mainly concentrating in southeast coastal areas in China. Squamous cell carcinoma, which is sensitive to radiation, is the most common pathological classification of NPC. Therefore, radiotherapy is the preferred treatment for the disease. In recent years, with the continuous improvement of local radiotherapy technology and comprehensive treatment methods, the overall survival rate of NPC patients has greatly increased. According to the current data, the 3-year overall survival rate of NPC patients is 82.3%; 5-year survival ranges from 59–76.1%; and the 10-year survival is 43% [1–4].

However, the complications of NPC patients after radiotherapy are still a great challenge and an urgent problem for clinicians. Among them, nasopharyngeal massive bleeding after radiotherapy (continuous bleeding of more than 300 ml, or bleeding of more than 100 ml [5–7]), is the most dangerous situation,

with a high mortality rate. Massive nasopharyngeal bleeding after radiotherapy therefore demands more attention from clinicians [5–8], though its incidence is not high. In order to explore the possible risk factors of massive hemorrhage after radiotherapy in NPC patients, we retrospectively analyzed the clinicopathological data of 539 patients with NPC after radiotherapy. Our findings provide a more reliable theoretical basis for clinical analysis and judgment of the probability and risk of nasopharyngeal hemorrhage in NPC patients after radiotherapy.

Methods

Inclusion and exclusion criteria

Inclusion criteria: ☐non-keratinized undifferentiated and differentiated carcinoma of the nasopharynx confirmed by pathology; ☐patients who had received radiotherapy for NPC; ☐patients who had received initial treatment without distant metastasis.

Exclusion criteria: ☐patients with other pathological types; ☐ patients who did not receive or did not complete radiotherapy for NPC; ☐patients with distant metastasis at the time of initial treatment; ☐ patients with incomplete clinical pathology and follow-up data.

Patient characteristics

From January 2005 to January 2015, 539 patients with NPC at our hospital met the study's inclusion criteria. Among them, 147 patients had received radiotherapy alone, and 392 patients had received radiotherapy with concurrent chemotherapy. The study ultimately included 428 males and 111 females with an average age of 47.4 years (range, 16-78 years). The study was approved by the Medical Ethics Committee at our hospital. Because of the retrospective nature of the study, patient consent for inclusion was waived.

Clinical and pathological factors

In this study, we mainly analyzed the following clinical and pathological factors: gender; age; T-stage; N-stage; pathological type; type of radiotherapy; synchronous chemotherapy; secondary-course radiotherapy; radioactive skull base osteonecrosis; diabetes, hypertension, or other systemic diseases; results of nasopharyngeal bacterial culture; nasopharyngeal tumor recurrence. Clinical stage was determined according to the Union for International Cancer Control (UICC) standard (8th Edition) [9, 10]. Pathological types were determined by hematoxylin-eosin (HE) staining. Cervical lymph node metastasis was determined by fine-needle aspiration cytology, and staging was determined based on the results of imaging examinations. The radiotherapy methods involved in this study included three-dimensional conformal intensity-modulated radiotherapy (IMRT) and conventional linear accelerator radiotherapy. Cases treated with concurrent chemotherapy also received 21-d cisplatin single-drug therapy. Eighteen cases with incomplete pathological data were included in this study. The original medical records were searched, and paraffin samples in the department of pathology were re-sectioned to supplement the data.

Follow-up

Patients with NPC after treatment were followed-up regularly by means of a return visit, investigation, and interviews by telephone or snail mail. Among 539 patients, 64 patients suffered from nasopharyngeal hemorrhage (all more than 400ml). The occurrence of nasopharyngeal hemorrhage ranged from 4 months to 7 years after radiotherapy (average 27.2 months after radiotherapy). Nine cases died at home or on the way to the hospital. Forty-six patients were successfully rescued, 41 of whom received arterial embolization or stent implantation. Patients were followed until the end of life.

Statistical analysis

SPSS20.0 software was used to analyze the relationship between the clinicopathological factors of NPC patients and the occurrence of nasopharyngeal hemorrhage after radiotherapy. Then logistic regression analysis (step by step) was performed for selected factors. The Kaplan-Meier method was used to analyze the correlation between patient survival and nasopharyngeal hemorrhage after radiotherapy.

Results

Among 539 patients with NPC, 64 (11.8%) had nasopharyngeal hemorrhage after radiotherapy. The clinical and pathological factors analyzed within groups included: gender; age; T-stage; N-stage; pathological type; type of radiotherapy; synchronous chemotherapy; secondary-course radiotherapy; radioactive skull base osteonecrosis; diabetes, hypertension, or other systemic diseases; results of nasopharyngeal bacterial culture; nasopharyngeal tumor recurrence. We found that there was a significant correlation between nasopharyngeal hemorrhage and secondary-course radiotherapy ($p < 0.01$), radioactive skull base osteonecrosis ($p < 0.01$), nasopharyngeal bacterial culture results ($p < 0.01$), and nasopharyngeal tumor recurrence ($p < 0.01$); No significant correlation with nasopharyngeal hemorrhage after radiotherapy was found for gender, age, N-stage, pathological type, type of radiotherapy, synchronous chemotherapy, diabetes, hypertension, or other systemic diseases ($p > 0.05$) (Table 1).

Table 1

Clinical and pathological characteristics of nasopharyngeal hemorrhage after radiotherapy for nasopharyngeal carcinoma

Clinicopathological factors	Hemorrhage	No hemorrhage
Gender		
Male	52(9.7)	377(69.9)
Female	12(2.2)	98(18.2)
Age		
< 40 years	14(2.6)	67(12.4)
40–60 years	35(6.5)	279(51.8)
> 60 years	15(2.8)	129(23.9)
Bacterial infection		
Yes	40(7.4)	264(49.0)
No	24(4.5)	211(39.1)
T-stage		
T1	13(2.4)	182(33.8)
T2	17(3.2)	179(33.2)
T3	25(4.6)	101(18.7)
T4	9(1.7)	13(2.4)
N-stage		
N0	16(3.0)	124(23.0)
N1	21(3.9)	187(34.7)
N2	20(3.7)	127(23.6)
N3	7(1.3)	37(6.9)
Pathological type		
Non-keratinized undifferentiated	41(7.6)	312(57.9)
Non keratinized differentiated	23(4.3)	163(30.2)
Radiotherapy methods		
linear accelerator	24(4.5)	169(31.4)

Clinicopathological factors		Hemorrhage	No hemorrhage
	Three-dimensional conformal intensity modulation	40(7.4)	306(56.8)
Concurrent chemotherapy			
	No	15(2.8)	120(22.3)
	Yes	49(9.1)	355(65.9)
Second radiotherapy			
	No	33(6.1)	432(80.1)
	Yes	31(5.8)	43(8.0)
Destruction or necrosis of skull base bone			
	No	10(1.9)	423(78.5)
	Yes	54(10.0)	52(9.6)
Systemic diseases			
	No	45(8.4)	351(65.1)
	Yes	19(3.5)	124(23.0)
Local recurrence			
	No	22(4.1)	415(77.0)
	Yes	42(7.8)	60(11.1)

Multivariate logistic regression analysis for the factors listed above showed that only radioactive skull base osteonecrosis was significantly associated with nasopharyngeal hemorrhage after radiotherapy (OR = 41.83, $p = 0.0001$, Table 2). Among 64 cases of nasopharyngeal hemorrhage, 55 cases were immediately sent to the hospital, and 9 cases died at home or on the way to the hospital. Among the 55 patients who were immediately sent to the hospital, 46 cases were rescued by successful nasal packing. Forty-one cases were detected by digital subtraction angiography (DSA), including 10 cases with bleeding from the external carotid artery that were treated with arterial embolization. There were 31 cases with internal carotid artery hemorrhage, including 6 cases that were treated with arterial embolization, and 25 cases that were treated with a covered stent. Kaplan-Meier survival analysis showed that the overall 3-year survival rate and 5-year survival rate were 26.6% and 12.2%, respectively (Fig. 1). Among 31 patients with internal carotid artery hemorrhage, the 1-year survival rate was 60.9%; the 3-year survival rate was 15.1%; there was no 5-year survival rate. Nineteen patients died of re-bleeding. The 5-year survival rate was 50% in patients with external carotid artery bleeding (Fig. 2). Among the 5 patients who did not

continue to receive treatment after successful rescue, 3 cases died of re-bleeding a few days later, and the other 2 cases were followed up for 3 years without any episode of re-bleeding.

Table 2. Logistic analysis of clinicopathological factors related to nasopharyngeal hemorrhage after radiotherapy for nasopharyngeal carcinoma

	Estimated value	Standard error	u-value	p-value	OR	95%CI
Constant terms	-3.934	1.053	3.735	0.0002		
Gender	0.626	0.420	1.489	0.1365	1.87	0.820-4.261
Age	-0.007	0.015	0.495	0.6204	0.99	0.964-1.022
T-stage	0.079	0.190	0.414	0.6787	1.08	0.746-1.569
N-stage	0.120	0.186	0.646	0.5182	1.13	0.783-1.624
Pathological type	-0.094	0.363	0.258	0.7960	0.91	0.447-1.855
Radiation methods	-0.443	0.371	1.194	0.2325	0.64	0.310-1.329
Concurrent chemotherapy	-0.389	0.420	0.926	0.3546	0.68	0.298-1.544
Second radiation	-0.343	0.603	0.568	0.5703	0.71	0.218-2.317
Bone destruction	3.734	0.505	7.388	0.0001	41.83	15.53-112.61
Systemic diseases	0.675	0.438	1.544	0.1226	1.96	0.834-4.632
Bacterial infection	0.097	0.380	0.255	0.7987	1.10	0.523-2.320
Nasopharyngeal recurrence	0.632	0.616	1.026	0.3048	1.88	0.563-6.295

Discussion

Radiotherapy is the preferred treatment for NPC. Radiation not only kills tumor cells, but also damages normal tissues and cells around the tumor. In NPC patients, the main cause of nasopharyngeal hemorrhage after radiotherapy is damage to adjacent blood vessels. Previous studies have shown that radiation may lead to vascular endothelial damage, resulting in elastic fiber rupture and increased

vascular wall fragility [11]. In addition, tissue necrosis in areas surrounding the tumor may impair the delivery of nutrition to the vascular wall, which may exacerbate any pre-existing damage and increase risk for vascular wall rupture and massive bleeding in the presence of infection.

In a case-control study, Chen et.al found that secondary-course radiotherapy and radiation-induced skull base osteonecrosis were key factors predicting carotid artery rupture syndrome after radiotherapy [12]. Results from the univariate analysis in our study showed that T-stage, secondary-course radiotherapy, radioactive skull base osteonecrosis, results of nasopharyngeal bacterial culture, and nasopharyngeal tumor recurrence were significantly correlated with nasopharyngeal hemorrhage. These results were similar to those reported by Chen et al. We found that T-stage was closely related to nasopharyngeal hemorrhage after radiotherapy. One reason for this observation may be tumor invasion of bone tissue and even arteries after T3 stage. In such cases, a high radiation dose during radiotherapy may cause bone necrosis, impairment of the nutrition supplied to bone, or direct radiation damage to blood vessels.

Secondary-course radiotherapy is performed to treat recurrent head and neck tumors after radiotherapy. It has been reported that this therapy achieves a good rate of local control. However, after application of this therapy, 32.5% of patients die of carotid artery rupture syndrome or carotid hemorrhage [13]. We also found that the incidence of nasopharyngeal hemorrhage increased significantly after the second course of radiotherapy. We speculate that an increase in radiation dose aggravates damage to the bone, mucosa, and blood vessels.

Wu et.al found that nasopharyngeal necrosis was closely related to infection after radiotherapy, and that lesions could erode the internal carotid artery and cause massive hemorrhage [14]. Our study found that patients with positive results on nasopharyngeal bacterial culture were more likely to experience nasopharyngeal hemorrhage. The toxins and enzymes released by bacteria may damage the arterial wall, especially in areas where necrosis affects the bone and mucosa, which aggravates tissue damage and causes bleeding.

The results of our univariate analysis indicated that the recurrence of nasopharyngeal tumor was closely related to nasopharyngeal hemorrhage. One possible reason is that recurrent nasopharyngeal tumor is more likely to invade damaged bone, and even directly destroy the vulnerable artery wall, after radiotherapy, resulting in massive hemorrhage.

Further logistic multivariate analysis showed that only radioactive skull base osteonecrosis was related to nasopharyngeal hemorrhage after radiotherapy, which indicated that destruction or necrosis of the skull base may be the decisive factor leading to nasopharyngeal hemorrhage after radiotherapy. The other four factors investigated appeared to act only as synergistic or influencing factors.

Previous studies have shown that platinum-based concurrent chemotherapy may improve the survival rate of NPC patients [15, 16] and may also cause damage to coagulation function and blood vessels [17]. However, our study did not find a clear correlation between treatment with chemotherapy drugs and nasopharyngeal bleeding. The presence of diabetes, hypertension, or other systemic diseases were

reported to lead to peripheral vascular lesions, which may increase the risk of bleeding in tissue with radiation-related damage. However, the results from our study indicated no significant correlation between such complications and nasopharyngeal bleeding after radiotherapy.

In NPC patients who have undergone radiotherapy, nasopharyngeal hemorrhage mostly involves the internal carotid artery or external carotid artery branch and a high mortality rate. Most patients die of hemorrhagic shock or asphyxia caused by the aspiration of blood fluid. The present study included 64 cases with massive hemorrhage, including 55 sent immediately to the hospital, and 46 rescued successfully. The successful rescue was 83.6%. After successful rescue, DSA should be performed to identify the vessel that caused the bleed. In the case of bleeding from the external carotid artery branch, vascular interventional embolization can be performed for hemostasis; tissue ischemia and necrosis can be avoided because collateral circulation is abundant. However, in the case of internal carotid artery hemorrhage, vascular interventional embolization or a covered stent may be used, depending on the pattern of intracranial artery vascularization. Jung et al. found that the average survival time in such patients could be increased by 9 months through the use of interventional therapy [18].

Mak et al. [19] analyzed 15 patients with massive hemorrhage caused by rupture of an internal carotid artery pseudoaneurysm after radiotherapy for NPC. Four patients underwent arterial embolization, 11 patients were implanted with covered stents, and bleeding was stopped in all cases. However, during the follow-up period, pseudoaneurysm occurred again in 2 cases, with cerebral infarction in 2 cases and brain abscess in 1 case. During an average follow-up of 13 months, the stent patency rate was 67%. There were no clinical symptoms in 3 cases with stent occlusion. Therefore, it is considered that good results are achieved with embolization and use of a covered stent. Tsang et al. [20] reached a similar conclusion. In our study, the rate of survival after external carotid artery branch bleeding was significantly higher than the rate of survival after internal carotid artery bleeding. Embolization of the external carotid artery branch therefore appears to be the more effective treatment strategy, because the embolization of internal carotid artery hemorrhage is associated with complications such as hemiplegia and cerebral infarction. Therefore, we elected to use the covered stent to achieve an immediate hemostatic effect. However, the covered stent is short, and the portion of the vessel wall that remains uncovered may be fragile due to radiotherapy, sometimes leading to a second massive hemorrhage and a low survival rate. In this study, 19 patients died of rebleeding after receiving a covered stent.

Conclusions

In conclusion, massive hemorrhage after radiotherapy in NPC patients is dangerous, with a poor prognosis. Necrosis or destruction of the skull base may increase the risk of nasopharyngeal hemorrhage. We should pay sufficient attention to the patient's condition and make sure that medical treatment is administered in an expedient fashion. After successful rescue, arterial embolization or stent implantation may prolong survival time.

List Of Abbreviations

NPC nasopharyngeal carcinoma

UICC Union for International Cancer Control

HE hematoxylin-eosin

IMRT intensity-modulated radiotherapy

DSA digital subtraction angiography

Declarations

Ethics Approval and consent to participate

This project was approved by the Ethics Committee of the 900th Hospital of Joint Logistic Support Force, PLA, China (approval no. 2016-021). Because of the retrospective nature of the study, patient consent for inclusion was waived.

Patient consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Wang MX and Chen XM conceived and designed, and supervised the study. Gong HX and Chen SY collected and analyzed the data. Yang Fan performed statistical analysis. All authors have read and approved the final version of the manuscript.

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Figures

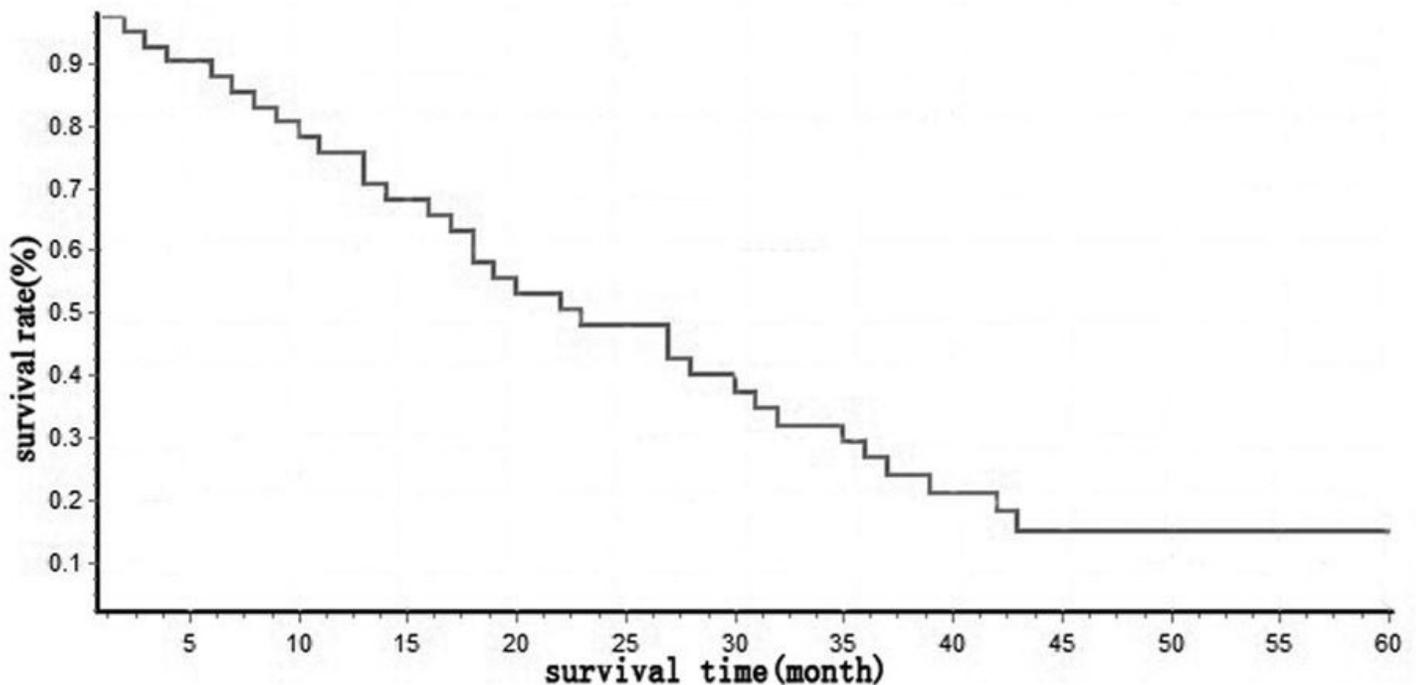


Figure 1

The overall survival rate of nasopharyngeal hemorrhage patients after radiotherapy.

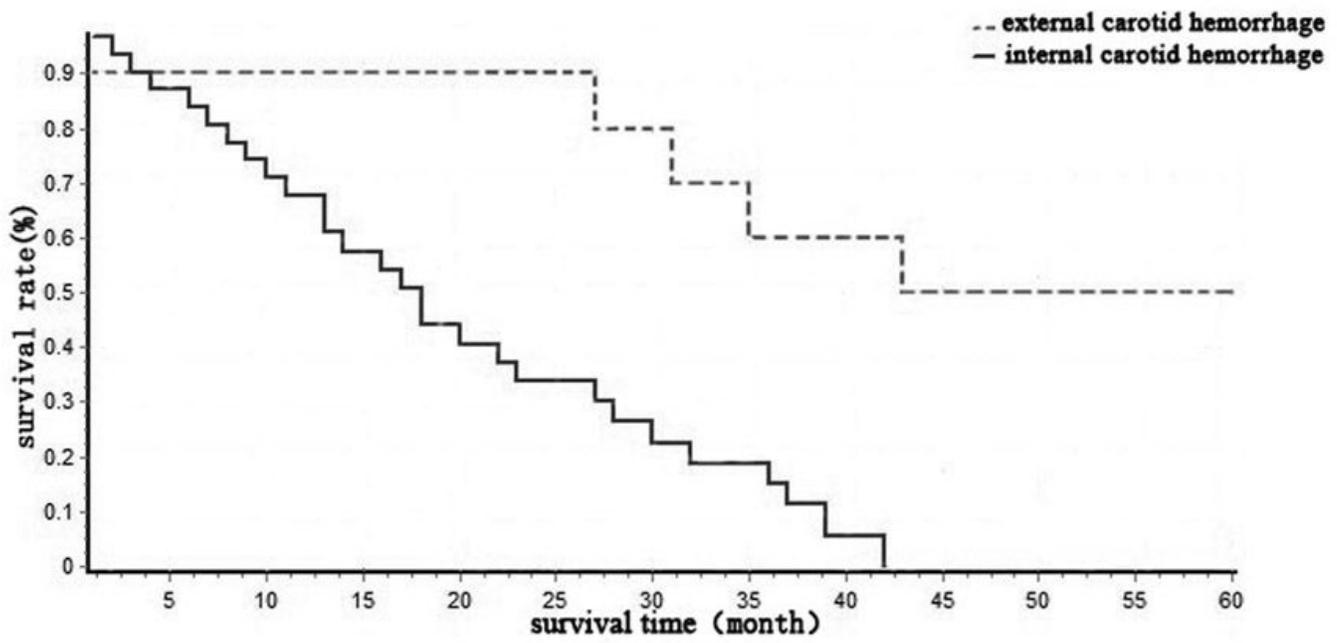


Figure 2

Comparison of survival rate between massive hemorrhage induced by external vs. internal carotid artery rupture.