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The value of preoperative radiotherapy in the treatment of locally advanced nasal cavity and paranasal sinus squamous cell carcinoma: A single institutional experience

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Introduction

The nasal cavity and paranasal sinus carcinomas (NPSCs) are relatively rare and account for only 3 to 5% of all head and neck cancer and less than 1% of all malignant tumors [1–3]. As a result of the special anatomical structure, most patients at diagnosis present with advanced stage disease. The advanced lesions usually have extensive invasion of adjacent critical structures including pterygopalatine fossa, orbit, optic nerve, skull base, and central nervous system, which adds further complexity to the treatment and accounts for the poor curative effects [4,5]. There are various histological types of NPSCs and squamous cell carcinoma (SCC) is the most common histological type. Due to the rarity of the disease and the variety of histological types, the current treatment strategies are mainly derived from retrospective analysis and population-based registry studies. Therefore, there is a lack of consensus regarding to the optimal treatment strategy for NPSCs. In general, complete resection should be pursued, while it is difficult to achieve for locally advanced disease. In this condition, multimodality treatment with surgery plus radiotherapy is the standard paradigm, previous studies have confirmed the clinical outcomes of comprehensive therapy is superior to that of single-modality therapy including surgery or definitive radiotherapy [6–10]. However, the optimal treatment combination and sequence are still controversial. Currently, the international mainstream recommendation tends to surgery followed by postoperative radiotherapy, while the application of preoperative radiotherapy plus surgery in our center also achieved good clinical outcomes.

To our knowledge, preoperative radiotherapy is able to shrink tumor volumes to achieve the purpose of down-staging, increase complete resection rate, reduce the risk of intraoperative spread of the tumor, as well as add the opportunity of organ preservation and functional integrity. Some retrospective studies clarified the advantages of preoperative radiotherapy in complete resection, organ preservation, and even survival outcome for other head and neck squamous cell carcinomas [11–13]. However, the value of preoperative radiotherapy in the comprehensive treatment for nasal cavity and paranasal sinus

Abbreviations: NPSCs, nasal cavity and paranasal sinus carcinomas; SCC, squamous cell carcinoma; NPSCCs, nasal cavity and paranasal sinus squamous cell carcinomas; LA-NPSCCs, locally advanced nasal cavity and paranasal sinus squamous cell carcinomas; pCR, pathologic complete response; CRT, conventional radiotherapy; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; Pre-RT, pre-operative radiotherapy; PORT, post-operative radiotherapy; OS, overall survival; LC, local control; DMFS, distance metastasis free survival; DFS, disease-free survival; ENI, elective nodal irradiation

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squamous cell carcinomas (NPSCCs) is still under debate. The first study directly compared the efficacy of preoperative and postoperative radiotherapy was published in 1965, which showed no significant differences between preoperative and postoperative radiotherapy [14]. For decades, only one small sample research from our institution in 1982 found out a significantly higher 5-year overall survival in preoperative RT group than that in postoperative RT group (64% vs 26%) [15]. This retrospective study mainly aimed to assess the clinical outcomes of preoperative and postoperative radiotherapy and further to explore the value of preoperative radiotherapy in the treatment for locally advanced nasal cavity and paranasal sinus squamous cell carcinomas (LA-NPSCCs).

Materials and methods

Patient selection

Our study retrospectively analyzed clinical data including 267 patients diagnosed with NPSCCs between January 1998 and December 2016 from National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences. The eligibility criteria were as follows: stage III-IVB NPSCCs; receipt of surgery plus radiotherapy; apart from distant metastasis; no new diagnosed malignant tumor in the previous 5 years; no more than 3 months on the interval time between surgery and radiotherapy. Other exclusion criteria included organ dysfunction; receipt of previous treatment (except diagnostic procedures); salvage radiotherapy or surgery performed after recurrence. Finally, 140 (52.4%) patients were recruited for this study (Fig.1). All patients had received a complete medical history, physical examination including head and neck dedicated examination, endoscopy, a computed tomography (CT) scan and/or magnetic resonance imaging (MRI) of the head and neck, chest X-ray/chest CT scan, and other staging procedures before primary therapy. The medical records and diagnostic images of all patients were reviewed, and all patients were restaged according to the American Joint Committee on Cancer 8th Edition (AJCC 8th). The pathologic complete response (pCR) was defined as no viable tumor cells were detectable in the primary tumor by histopathology. All pathological sections were checked by at least two pathologists to determine whether pCR was achieved or not. Surgical margin and degree of resection were determined by reviewing surgical records and pathological reports. This study was approved by the local ethics committee.

Treatment planning

The primary treatment to all patients was determined by head and neck multidisciplinary team. Once primary tumor encroached on pterygopalatine fossa, orbital contents or orbital apex, it was difficult to completely remove and preserve the integrity of organ function. If these conditions were detected by preoperative examination, preoperative radiotherapy plus surgery is prior to be recommended. If pterygopalatine fossa, orbit cavity invasion, or positive margin were found during operation, or confirmed by postoperative pathologic examination, postoperative radiotherapy must be performed.

Surgical methods included open surgery and endoscopic surgery. Open craniofacial resection, lateral rhinotomy and maxillectomy were the mainstay of open surgery. Fifty-three patients were treated with conventional radiotherapy (CRT), 3 patients with three-dimensional conformal radiotherapy (3D-CRT), and 84 patients with intensity-modulated radiotherapy (IMRT). The radiation doses varied between treatment modalities: in pre-operative radiotherapy (Pre-RT) group, the median dose was 60 Gy (range: 48–70 Gy), while in post-operative radiotherapy (PORT) group, the median dose was 68 Gy (range: 40–80 Gy). The dose fractionation of radiotherapy ranged from 1.9 to 2.24 Gy (median dose: 2.0 Gy). Radiation was delivered with a continuous course of once-daily, 5-days-per-week treatment for all patients. Elective nodal irradiation (ENI) was routinely delivered to patients with T3-T4 lesions and/or positive cervical lymph nodes. For patients with invasion of the midline structure, bilateral neck elective nodal irradiation was generally performed.

In the case of obvious tumor necrosis or large volume indicated by imaging examination, we preferred to apply chemotherapy drugs to enhance sensitivity during radiotherapy. In addition, concurrent chemotherapy was also applied for patients with extranodal extension and positive surgical margin with consideration of patient tolerance. In this study, a total of 39 patients were treated with cisplatin or paclitaxel during radiotherapy. Among them, two patients received 120 mg

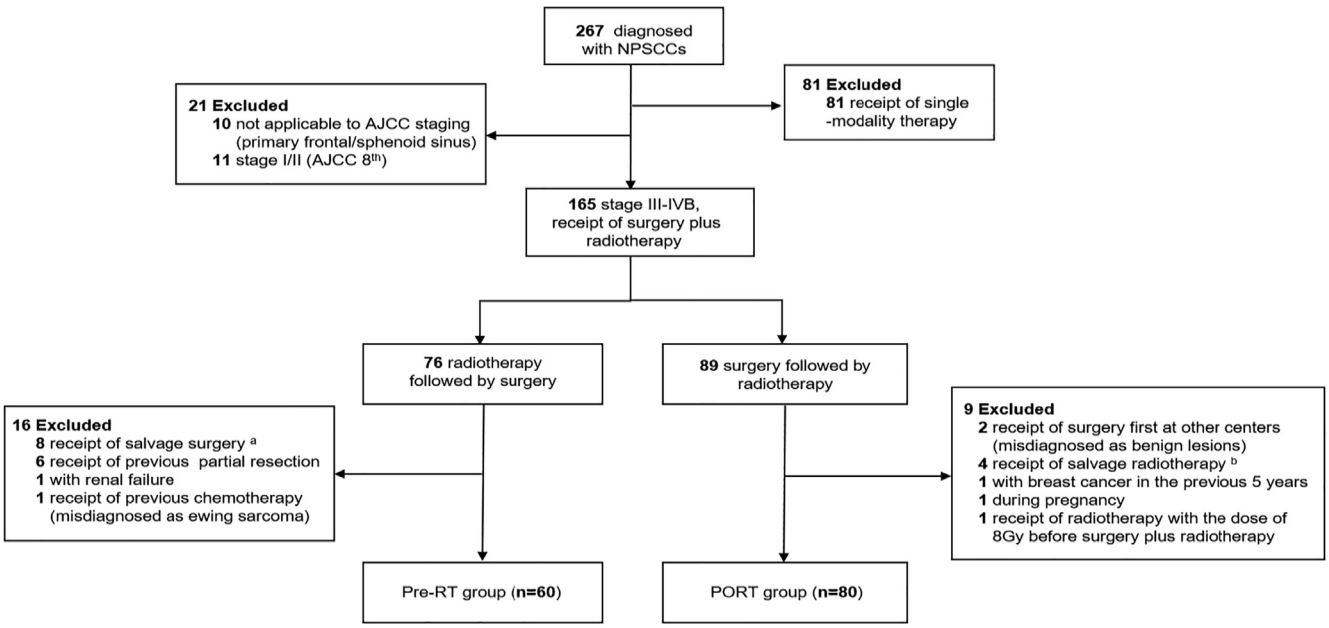

Fig. 1. Enrollment diagram. (a) Three declined to undergo surgery and were performed salvage surgery after disease progression; the remaining 5 cases were performed salvage surgery because of without tumor control after definitive radiotherapy. (b) Four cases declined to receive post-operative radiotherapy and underwent radiotherapy after disease progression. Abbreviation: NPSCCs: nasal cavity and paranasal sinus squamous cell carcinomas; Pre-RT: preoperative radiotherapy; PORT: postoperative radiotherapy.

cisplatin given as intra-arterial infusion weekly for 4 cycles, two received 30 mg intravenous paclitaxel weekly for 5–6 cycles, and the remaining patients were treated with 80–100 mg/m^2 intravenous cisplatin every 3 weeks for 2–3 cycles or 50–60 mg intravenous cisplatin weekly for 5–6 cycles.

Statistics

The endpoints of the study were overall survival (OS), local control (LC), distance metastasis free survival (DMFS) and disease-free survival (DFS), which were measured from the date of primary treatment until the documented first failures. Tumor response was classified according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Acute and late radiotherapy toxicities were assessed with the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity scoring criteria[16]. Differences between patient characteristics were analyzed using chi-square test for categorical variables and independent-sample test for continuous variables. The actuarial survival rate was calculated using the Kaplan-Meier method, and the differences were compared using log-rank tests. A two-tailed P value < 0.05 were considered statistical significance. Univariate analysis was performed to search for potential prognostic factors by using a log-rank test. Multivariate analysis using the Cox proportional hazard model was performed to identify independent predictors among the various potential prognostic factors. All statistical analyses were performed using SPSS 22.0 software.

Results

Baseline characteristics

In the entire cohort, the male-to-female ratio was 3.4:1, and the median age was 54 (16–83) years-old. According to the distribution of AJCC system, stage IV accounted for 80.7% of our cohort. The T4b disease accounted for 30% of cases in preoperative radiotherapy group, while 26.3% of cases were classified into T4b staging in postoperative radiotherapy group. The lymph node metastasis was confirmed in 27 patients (19.3%) on initial diagnosis (Supplementary Appendix summarized the distribution of lymph node metastases at the time of first presentation). The comparison of baseline characteristics between preoperative and postoperative groups was shown in Table 1.

Complete resection and complete response

In terms of degree of resection, 61.4% of patients (86/140) in our cohort achieved complete resection of the tumor. The complete resection rate of Pre-RT group was 93.3% (56/60), while that of PORT group was 38.0% (30/79). There was significantly difference between the two treatment groups (P value < 0.001). Among the 34 patients with gross tumor residual in PORT group, 18 patients achieved clinical complete response which were assessed by MRI or CT at the end of postoperative radiotherapy. In the Pre-RT group, 16 cases achieved clinical complete response after completing preoperative radiotherapy, finally 33.3% of patients (20/60) achieved pathologic complete response through pathological examination. The survival results of patients with and without pathologic complete response were shown in Supplementary Appendix. Compared to the non-pCR group, the pCR group achieved statistically higher 5-year OS rate (79.4% vs 58.1%, P value = 0.034), LC rate (89.7% vs 58.3%, P value = 0.013), DFS rate (79.7% vs 52.3%, P value = 0.018), while there was similar 5-year DMFS rate between the two groups (P value = 0.792) (The distribution of resection status and clinical tumor response between two groups was summarized in Supplementary Appendix).

Table 1
Comparison of baseline characteristics between groups.

Characteristics	Pre-RT group N = 60 (%)	PORT group N = 80 (%)	p-value
Gender			
Male	45 (75.0)	63 (78.7)	0.601
Female	15 (25.0)	17 (21.3)	
Age, years			
> 54	31 (51.7)	35 (43.8)	0.353
≤54	29 (48.3)	45 (56.2)	
Primary site			
Nasal cavity	9 (15.0)	30 (37.5)	0.009
Maxillary sinus	45 (75.0)	41 (51.3)	
Ethmoid sinus	6 (10.0)	9 (11.3)	
Orbital contents/apex invasion			
Yes	29 (48.3)	24 (30.0)	0.027
No	31 (51.7)	56 (70.0)	
Pterygopalatine fossa invasion			
Yes	25 (41.7)	29 (36.2)	0.515
No	35 (58.3)	51 (63.8)	
T stage			
T2-3	10 (16.7)	23 (28.8)	0.096
T4	50 (83.3)	57 (71.3)	
N stage			
N+	16 (26.7)	11 (13.8)	0.053
N0	44 (73.3)	69 (86.2)	
TNM stage (AJCC 8th)			
III	6 (10.0)	21 (26.2)	0.016
IVA/IVB	54 (90.0)	59 (73.8)	
Radiation technology			
IMRT	28 (46.7)	56 (70.0)	0.005
2D/3DCRT	32 (53.3)	24 (30.0)	
Radiation dose, EQD2			
60–66 Gy	15 (25.0)	12 (15.4)	< 0.001
> 66 Gy	11 (18.3)	51 (65.4)	
≤60 Gy	34 (56.7)	15 (19.2)	
Concurrent chemotherapy			
Yes	19 (31.7)	20 (25.0)	0.384
No	41 (68.3)	60 (75.0)	
Surgical approach			
Open surgery	60 (100.0)	59 (73.8)	< 0.001
Endoscopic surgery	0 (0.0)	21 (26.2)	

Abbreviation: 2D/3DCRT: Conventional Radiotherapy/Three-Dimensional Conformal Radiotherapy;
IMRT: Intensity-Modulated Radiotherapy; EQD2: Equivalent Dose in 2 Gy/f.

Organ preservation

A total of fifty-three patients (37.9%) in the entire cohort had infiltrated the orbital contents or orbital apex, 38 of them (71.7%) underwent organ preservation, while orbital exenteration was performed in remaining fourteen patients (Table 2). The actual orbital content retention rate was defined as the percentage of orbital content that was

Table 2
Treatment factors and results on the cohort with invasion of orbital contents or apex.

	Pre-RT group N = 29	PORT group N = 24	P value
Radiation technology			
2D or 3DCRT/IMRT	16/13	10/14	0.328
Radiation dose (median: 60 Gy)			
> 60 Gy/≤60 Gy	6/23	14/9[a]	0.003
Concurrent chemotherapy			
Yes/No	8/21	6/18	0.832
Surgical approach			
Endoscopic/Open	0/29	4/20	0.022
Orbital content preservation			
Exenteration [b]	2 + 3	8 + 2	0.049
Retention	24	14	

[a] There was one case with absent radiotherapy dose record.
[b] Primary surgery + Salvage surgery.

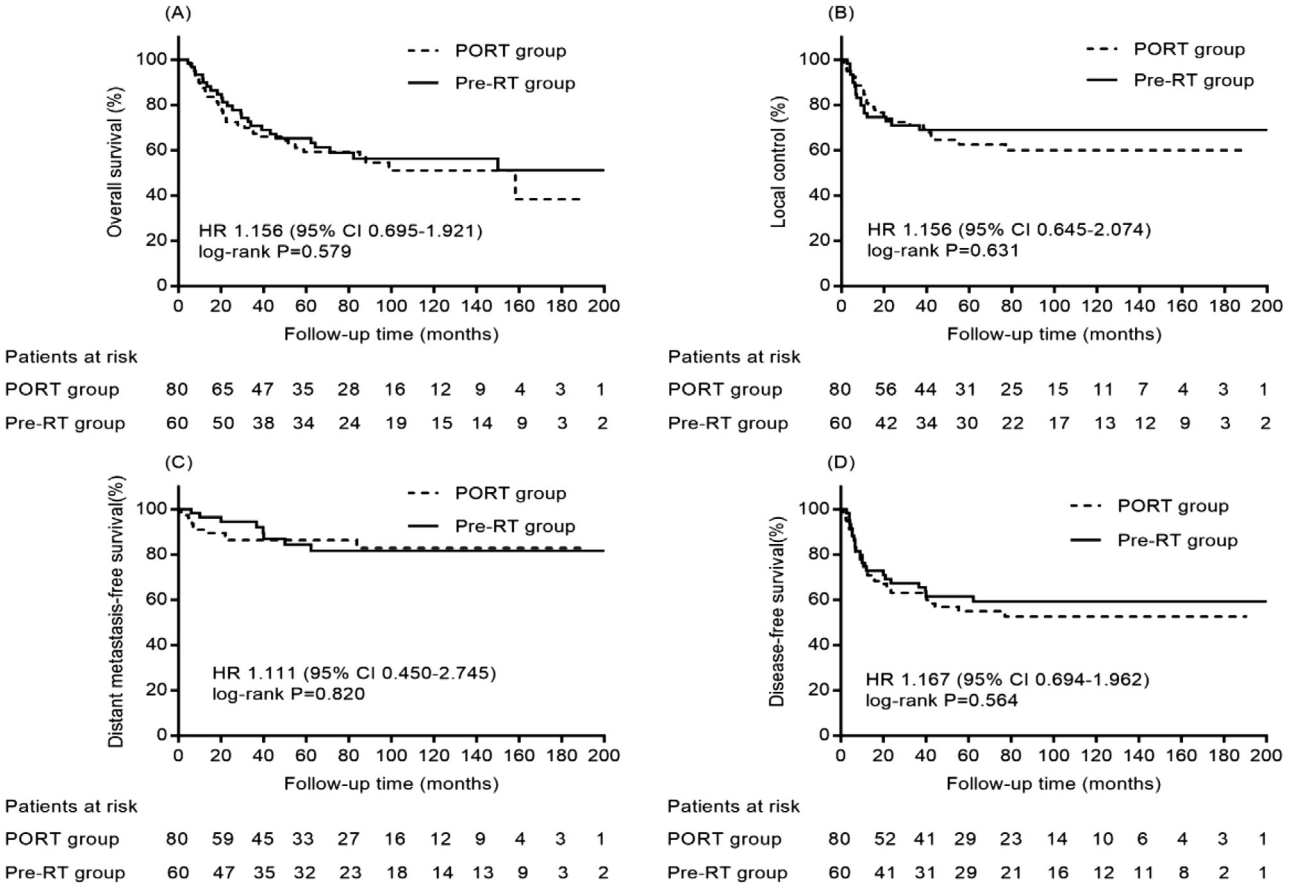

Fig. 2. Survival between preoperative group and postoperative group: (A) overall survival; (B) local control; (C) distant metastasis-free survival; (D) disease-free survival.

not removed during primary surgery or salvage surgery due to disease recurrence. The actual orbital content retention rate in Pre-RT group was 82.8% (24/29), while that in PORT group was 58.3% (14/24). There was significantly statistical difference between the two groups (P value = 0.049). In the cohort with invasion of orbital contents or apex, the 5-year OS rate of orbital exenteration and orbital retention subgroup were 52.5% and 39.1% respectively (P value = 0.477).

Survival outcomes and prognostic analysis

With a median follow-up time of 92.3 months (range: 4–230 months), the 5-year OS, LC, DMFS, and DFS of the entire cohort were 62.0%, 65.5%, 85.4%, and 57.8%, respectively. The 5-year OS, LC, DMFS and DFS of Pre-RT group were 65.3%, 69.0%, 84.4%, and 61.4%, while those of PORT group were 59.3%, 62.6%, 86.4%, and 55.0%, respectively. There was no statistical difference between the two groups (P value > 0.05) (Fig.2). The results of the univariate and multivariate analysis of prognostic factors for overall survival were reported in Table 3. On the univariate analysis, the positive prognostic factors for 5-year OS were age older than 54 years, stage IV, T4 lesion, orbital contents/apex invasion and non-complete resection. On multivariate analysis, age older than 54, orbital contents/apex invasion, and non-complete resection were independent adverse prognostic factors for 5-year OS (P value < 0.05).

Failure patterns

By the end of the last follow-up visit, fifty-eight patients (41.4%) had developed treatment failure, and 82.8% of them occurred within 2 years of follow-up. In the entire failure cohort, 46 patients (79.3%) experienced local recurrence, 11 patients (19.0%) developed regional recurrence, and 19 patients (32.8%) failed at distant metastasis. The comparison of failure patterns between the two groups was displayed in Fig.3. Compared with the postoperative radiotherapy group, the preoperative radiotherapy group did not reach statistical differences in local recurrence rate (80.0% vs 78.3%, P value = 0.873), regional failure rate (25.7% vs 8.7%, P value = 0.106), and distant failure rate (31.4% vs 34.8%, P value = 0.790). The 11 regional failures included level Ib (n = 4), level II (n = 8), level III (n = 2), supraclavicular fossa (n = 1) metastases. Distant metastasis was observed in various sites and the lung was the most common site (n = 15). Other sites of distant metastasis included mediastinal lymph node (n = 3), bones (n = 2), parotid gland (n = 2), pleura (n = 1), liver (n = 1), and brain (n = 1).

Treatment complication and toxicities

Treatments were relatively well tolerated among patients in both groups. The surgical complications in Pre-RT group were as follows: skin fistula (n = 2), postoperative infection (n = 2), and hemorrhage (n = 1). No one died of therapeutic complication in preoperative radiotherapy group. Relatively, the surgical complications in PORT group were as follows: skin fistula (n = 2), postoperative infection (n = 1), cerebrospinal fluid leakage (n = 1), and post-operative blindness (n = 1). One patient in the postoperative radiotherapy group died of postoperative reinfection of residual cavity. The comparison of acute and late radiotherapy toxicities between groups were summarized in Table 4. No grade 5 lethal toxicity was found in both groups. Regarding to radiotherapy compliance, two patients in the PORT group discontinued radiotherapy owing to grade 4 acute mucositis. In contrast, all patients in the Pre-RT group completed preoperative

Table 3
Results of univariate and multivariate analyses of prognostic factors for OS.

Characteristics	Univariate analysis			Multivariate analysis		
	5-yr OS (%)	$\chi 2$	p-value	HR	95% CI	p-value
Gender						
Male	63.4	0.941	0.332	0.575	0.304–1.088	0.089
Female	56.3					
Age, years						
> 54	51.8	4.178	0.041	2.793	1.532–4.983	0.001
≤54	71.7					
Primary site						
Nasal cavity	66.0	0.085	0.771	0.986	0.491–1.981	0.968
Paranasal sinus	60.6					
Orbital content/apex invasion						
Yes	43.1	15.970	< 0.001	3.146	1.783–5.551	< 0.001
No	73.6					
Pterygopalatine fossa invasion						
Yes	64.8	0.299	0.584	0.917	0.519–1.620	0.765
No	60.5					
T stage						
T2-3	83.8	8.622	0.003	–	–	–
T4	55.4					
N stage						
N+	65.5	0.278	0.598	0.860	0.421–1.758	0.680
N0	61.1					
TNM stage (AJCC 8th)						
III	84.4	6.980	0.008	–	–	–
IV	56.6					
Radiotherapy technology						
IMRT	62.2	0.001	0.976	1.654	0.796–3.437	0.177
2D/3DCRT	61.4					
Radiation dose, EQD2						
60–66 Gy	62.4	0.808	0.668			0.867
> 66 Gy	60.2			0.778	0.310–1.951	0.593
≤60 Gy	63.9			0.869	0.377–2.001	0.741
Concurrent chemotherapy						
Yes	70.1	0.265	0.607	0.766	0.387–1.517	0.445
No	59.0					
Surgical methods						
Open surgery	61.5	0.109	0.742	1.635	0.692–3.862	0.262
Endoscopic surgery	65.5					
Degree of resection						
Non-complete resection	50.2	6.178	0.013	2.591	1.205–5.568	0.015
Complete resection	70.1					
Treatment sequence						
Pre-RT + Surgery	59.3	0.308	0.579	1.086	0.493–2.393	0.838
Surgery + PORT	65.3					

Abbreviation: 2D/3DCRT: Conventional Radiotherapy/Three-Dimensional Conformal Radiotherapy; IMRT: Intensity-Modulated Radiotherapy; EQD2: Equivalent Dose in 2 Gy/f. Pre-RT: Preoperative Radiotherapy; PORT: Postoperative Radiotherapy.

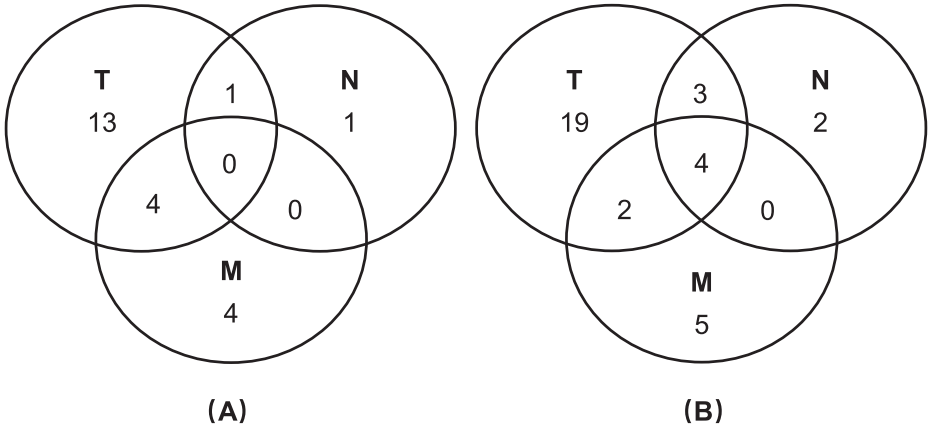

Fig. 3. The comparison of failure patterns between groups: (A) Preoperative radiotherapy group; (B) Postoperative radiotherapy group.

Table 4
Acute and late radiotherapy toxicities between groups.

	Pre-RT group			PORT group		
	Grades 0	Grades 1–2	Grades 3–4	Grades 0	Grades 1–2	Grades 3–4
Acute radiotherapy						
Mucositis	2 (5.4%)	29 (78.4%)	6 (16.2%)	3 (4.9%)	43 (70.5%)	15 (24.6%)
Dermatitis	1 (2.7%)	35 (94.6%)	1 (2.7%)	4 (6.5%)	55 (90.2%)	2 (3.3%)
Dry mouth	7 (18.9%)	30 (81.1%)	–	16 (26.2%)	45 (73.8%)	–
Odynophagia	25 (67.6%)	11 (29.7%)	1 (2.7%)	33 (54.1%)	26 (42.6%)	2 (3.3%)
Hematologic toxicities [a]	27 (73.0%)	10 (27.0%)	0 (0.0%)	38 (62.3%)	17 (27.9%)	6 (9.8%)
Late radiotherapy						
Temporal lobe necrosis	32 (94.2%)	1 (2.9%)	1 (2.9%)	38 (92.7%)	2 (4.9%)	1 (2.4%)
Impaired vision	21 (61.8%)	5 (14.7%)	8 (23.5%)	26 (63.4%)	7 (16.1%)	8 (19.5%)
Hearing loss	26 (76.5%)	4 (11.8%)	4 (11.7%)	32 (78.0%)	5 (12.2%)	4 (9.8%)
Trismus	29 (85.3%)	5 (14.7%)	–	37 (90.2%)	4 (9.8%)	–
Dry mouth	19 (55.9%)	15 (45.1%)	–	21 (51.2)	20 (48.8%)	–

Abbreviation: NA: not acquired; Pre-RT: Preoperative Radiotherapy; PORT: Postoperative Radiotherapy.
[a] This refers leucopenia, neutropenia, anemia and thrombocytopenia.

radiotherapy as planned.

Discussion

The treatment of NPSCCs is an enormous challenge to both surgeons and radiotherapists for several decades. With advances in surgery and radiation technology, the clinical outcomes have been unsatisfactory. As far as we know, this is the latest study to assess the clinical outcomes of preoperative and postoperative radiotherapy. At the same time, our study shows the advantages of preoperative radiotherapy in complete resection, pathologic complete response, and orbital content retention for LA-NPSCCs.

In our study, the male-female ratio of population was nearly 3.4:1, which is higher than the 2:1 ratio reported in other studies [3]. The maxillary sinus were the most common sites in concordance with the literature. The median age of our cohort was 54 years, which is comparable to those reported previously. The lymphatic metastasis at diagnosis occurs in 4–30% of patients with NPSCCs[10,17,18]. Similarly, the lymph node metastasis rate of our cohort at the initial diagnosis was 19.3%. Ipsilateral single-site lymph node metastasis was most likely to occur, and Level Ib and II regions were the most common metastases. Therefore, this study is comparable with other studies in terms of demographic and clinical characteristics.

Regarding survival outcomes, most authors reported the 5-year OS rate of NPSCs had a wide range from 30% to 67%[19–24]. In concordance with these reports, the 5-year OS rate our entire cohort was up to 62%. Despite the high proportion of T4 or stage IV, we observed an excellent overall survival in both pre- and postoperative radiotherapy groups. Similarly, the entire cohort also achieved good LC, DMFS, and DFS rates. In addition to this study, several studies also tried to explore the optimal treatment pattern of NPSCs. Robin et al. analyzed the 11,160 patients from NCDB database and showed patients treated with adjuvant therapy and neoadjuvant therapy had improved survival outcomes compared to patients treated with single-modality surgery, but failed to compare adjuvant therapy and neoadjuvant therapy [6]. Howard et al found that whether radiotherapy was performed before or after craniofacial resection, there was no statistical difference on survival outcomes for those patients receiving combined therapy [25]. However, whether the baseline data between the two groups were balanced was not mentioned in the article. Ashraf M et al conducted an analysis compared the results of various approaches to treatment about 379 patients with maxillary sinus squamous cell carcinoma, which showed patients received PORT had better 5-year OS and LC (63.5% vs 47%; 65.8% vs 38.9%), but there was higher proportion of T4 lesion in Pre-RT group (35.6% vs 18.7%) [26].

Although our study revealed no statistical difference on 5-year OS, LC, DMFS and DFS between Pre-RT and PORT group, it should not be ignored that the patient characteristics between both groups were not well balanced. In fact, it is difficult to well balance baseline characteristics between groups due to the limitation of retrospective study. More adverse prognostic factors including orbital contents/apex invasion and stage IV were found in the preoperative radiotherapy group, which were confirmed by multivariate analysis. Although the significant difference was found in the primary site, radiotherapy technology, radiation dose and surgical method between both groups, neither univariate analysis nor multivariate analysis showed that these factors significantly affected the overall survival. According to AJCC system, invasion of orbital content is classified as T4a and invasion of orbital apex is classified as T4b. Therefore, in order to avoid the confounding of the above factors, we only included orbital content/apex invasion and lymph node metastasis combined with other variables into multivariate analysis. On the present multivariate analysis model, older age, non-complete resection and orbital content/apex invasion were independent prognostic factors. However, orbital content/apex invasion has the higher weight on Cox-regression model (HR: 3.146 vs 2.591), which may partly explain why survival was not improved in the preoperative radiotherapy group with a higher complete resection rate. The other possible reason is that postoperative radiotherapy made a considerable proportion of cases with gross tumor residual achieve clinical complete response.

The pCR was a good prognosis predictor, which had been confirmed in other head and neck squamous cell carcinomas [27]. Kreppel M et al. analyzed 53 patients with squamous cell carcinoma of maxillary sinus. Patients who achieved pathological complete response after neoadjuvant chemoradiotherapy had a significantly higher 5-year overall survival rate than patients with incomplete response or nonresponse (70% vs 26%, P = 0.021) [23]. In concordance with literature, the pCR subgroup had statistically higher 5-year OS, LC, DFS and similar 5-year DMFS. Apparently, patients who achieved pCR not only improved local control, but also converted this advantage into survival benefit. In this study, one third of patients from Pre-RT group achieved pathologic complete response, which was higher than 21% reported by Kreppel M et al. Another small sample study included 79 patients of nasal and paranasal sinus tumors, who underwent preoperative chemoradiotherapy, the pathological complete response rate was 48% [28]. There is a lack of valid biomarkers that can predict individual response to radiotherapy, which needs to further research in the future.

Previous studies reported considerable orbital content retention rate after neoadjuvant therapy. However, these results were mostly from some small sample analyses and seldomly compared to other treatment modalities. Only 32% of patients in the preoperative radiotherapy group received concurrent chemotherapy, the orbital content retention

rate still reached 85.7% after preoperative radiotherapy, which was comparable to that reported in previous literature. Chen et al. analyzed 28 cases of T4b stage of NPSCCs treated with induction chemotherapy followed by concurrent chemoradiotherapy, the effective orbital preservation rate was up to 77.8% [29]. In a small sample study from South Korea, 82.7% (14/17) of patients with T4a or T4b NPSCCs retained eyeballs after induction chemotherapy and surgery [30]. Fernstrom E.et al. reported a low orbital exenteration rate of 7% in the research included 73 cases of locally advanced nasal and paranasal sinus tumors treated with preoperative chemoradiotherapy [28]. Previous studies agreed on resection of the tumors without orbital exenteration when tumors invasion was only limited to orbital bone or periosteum [31,32]. Once the tumor broke through orbital bone wall or periosteum, and encroached upon orbital contents or orbital apex, it was usually difficult to retain the eyeball. In this condition, many studies had revealed different results on overall survival and local control, even when adjuvant radiotherapy was given after the preservation of the eyeball [31,33]. Based on the above, we calculated the proportion of organ preservation in patients with orbital content/apex invasion. Apparently, preoperative radiotherapy significantly improved orbital content retention rate by shrinking tumor volumes and T-down-staging, although the total dose of preoperative radiotherapy was lower. After a long-term follow-up, there was no significant difference on the degree of visual impairment between the two groups, suggesting that preoperative radiotherapy not only improved the chance of orbital content retention, but also retained the long-term function of the visual organ. More importantly, orbital content retention did not significantly reduce overall survival.

According to the distribution of failure patterns, the both groups mainly developed single-pattern failure, and local recurrence was the predominant failure pattern, which indicated the different treatment patterns did not lead to significant differences in failure pattern. Based on previous studies, the local recurrence rate was between 31.5% and 69.2% [4,21,26,34]. The eighteen patients (78.3%) in the preoperative group and 28 patients (80.0%) in the postoperative group developed local recurrence. Most of the patients presented with very locally advanced lesions encroaching on the neighboring structures (T4 disease accounting for 76.4% of patients). This might be one of the possible reasons for the higher local recurrence rate in our study. The regional failure rate in the preoperative radiotherapy group was not only lower than that in the postoperative radiotherapy group, but also lower than 18%-27% reported in the previous literatures [4,21,26,34]. We also found 10 patients (90.9%) had lymph node metastasis before treatment in patients with cervical lymph node failure, which might indicate lymph node metastasis before treatment was associated with regional failure. Consistent with regional failure rate, the positive rate of regional lymph nodes in preoperative radiotherapy group was also lower than that in postoperative radiotherapy group (P value = 0.053). As for the distant failure rate, both groups were almost 30% in concordance with 11% to 35% reported in the literature [4,21,26,34].

This study retrospectively analyzed cases over 18 years, the records on acute and late toxicities were partly absent, making it difficult to analyze adverse events for entire cohort. Therefore, we conducted a statistical analysis of the toxicity records for all available cases. We found no significant difference in either acute or late radiotoxicities between the two groups. Radiation toxicity was related to radiation dose and fractionation. Theoretically, the preoperative radiotherapy group should have fewer treatment-related toxicities due to the lower radiation dose. However, a higher proportion of patients in the preoperative radiotherapy group received conventional radiation, which explained for the absence of significant differences in treatment-related toxicities between the two groups. In terms of treatment compliance, all patients completed preoperative radiotherapy followed by as planned, which suggested preoperative radiotherapy appeared to have better compliance.

We acknowledge that our study has some limitations. First, this study is mainly derived from retrospective analysis, which has the drawback of inherent selection bias. Furthermore, due to the limitation of retrospective analysis, the records of adverse reactions are not perfect, it is difficult to completely compare the therapeutic side effects between the two groups. Nevertheless, as the latest study to assess clinical outcomes of preoperative and postoperative radiotherapy, we believe that the current analysis did provide some useful information to the therapy of the nasal cavity and paranasal sinus carcinomas.

Conclusions

In the absence of randomized controlled studies, this study showed the advantages of preoperative radiotherapy. On the basis of multimodality therapy becoming standard paradigm for LA-NPSCCs, preoperative radiotherapy significantly improved complete resection rate and the chance of orbital content retention. More importantly, preoperative radiotherapy did not result in additional operative complications and was well tolerated. Therefore, preoperative radiotherapy followed by surgery might be desirable for LA-NPSCCs, especially for those with organ preservation intention.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper..

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.104512.

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