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Sinonasal Malignancies with Orbit Invasion: SNU Experience

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Abstract

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Sinonasal cancers often invade the orbit. The approach to treating sinonasal cancer invading the orbit can vary depending on the expertise, medical center, and the extent of the invasion. The definitive treatment strategy, whether it involves preserving the orbit or not, varies on a case-by-case basis and leads to different prognosis outcomes for the disease. Currently, a multimodal treatment approach, which includes surgery, chemotherapy, radiotherapy (RT), or concurrent chemoradiotherapy (CCRT), is frequently employed for sinonasal cancers. This study aims to evaluate the clinical characteristics of sinonasal cancers with orbit invasion.

We conducted a retrospective review of patients with primary sinonasal cancers invading the orbit who were treated at Seoul National University Hospital and Seoul National University Bundang Hospital between 2009 and 2018. We examined factors such as cancer pathology, the extent of orbit invasion, treatment strategies, recurrence rates, and survival rates.

Out of 141 patients, the most common pathology observed was squamous cell carcinoma (SqCC) (68 patients, 48.2%). Patients with SqCC exhibited a significantly lower disease-free survival (DFS) rate (5-year DFS 35.1±7.2%) compared to other pathologies. Overall survival (OS) and DFS rates did not significantly differ based on the grade of orbit invasion. In subgroup analysis of SqCC cases, when tumor resection with orbit preservation was performed as the definitive treatment, DFS was significantly longer compared to cases where surgery was not the definitive treatment (RT, CCRT). There was no significant difference in DFS between those who underwent orbit exenteration as the definitive treatment and those who underwent tumor resection with orbit preservation as the definitive treatment.

Tumor resection with orbit preservation as the definitive treatment appears to be the preferred approach, leading to prolonged DFS while ensuring survival in cases of SqCC with orbit invasion. Additionally, as the grade of orbit invasion increases, performing tumor resection with orbit preservation, and as it decreases, opting for treatments without surgery as the definitive treatment, may be a more favorable approach for sinonasal cancer compared to treatments associated with significant disability, such as orbit exenteration.

Keyword : Nasal Cancers, Orbit, Survival Analysis, Disease-Free Survival, Mortality
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Chapter 1. Introduction

1.1. Study Background

Sinonasal cancer is a highly uncommon malignant tumor, comprising approximately 3% of head and neck tumors(Maghami and Kraus 2004; Turri-Zanoni, et al. 2015). The predominant pathology associated with sinonasal cancer is squamous cell carcinoma (SqCC)(Dulguerov, et al. 2001; Maghami and Kraus 2004). Sinonasal cancer is often diagnosed at advanced stages because it can remain asymptomatic until the tumor invades or closely approaches the skull base, nerves, orbit, or palate(Waldron and Witterick 2003). Historically, the standard treatment for sinonasal cancer involved the en-bloc resection of the primary tumor. However, this approach can be highly invasive in certain cases and may result in unfavorable cosmetic outcomes. Particularly in cases involving orbital invasion, en-bloc resection may necessitate orbit exenteration, significantly impacting a patient's quality of life. Consequently, radiotherapy (RT) and concurrent chemoradiotherapy (CCRT) have emerged as alternative treatment options and have been employed in selected cases(Forastiere, et al. 2003; Haddad and Shin 2008; Kuo and Lin 2022; Pignon, et al. 2009; Tobias, et al. 2010). Additionally, there is evidence suggesting that induction chemotherapy (CTx) can downstage advanced sinonasal cancers and facilitate eyeball preservation during treatment(Ock, et al. 2016). However, orbit invasion is recognized as a poor prognostic indicator, leading to debates regarding the inclusion of surgery as the definitive treatment(Carrillo, et al. 2005; Ganly, et al. 2005; Lisan, et al. 2016; Suarez, et al. 2004). Furthermore, there is ongoing controversy regarding the choice of surgical technique, specifically between tumor resection surgery with orbit exenteration and tumor resection surgery with orbit preservation(Howard, et al. 2006;

Imola and Schramm 2002; Lisan, et al. 2016; Shin, et al. 2022). Typically, indications for orbit exenteration encompass the involvement of structures such as the medial rectus muscle, optic nerve, ocular bulb, or the skin near the eyelid(Iannetti, et al. 2005; Imola and Schramm 2002). However, for SqCC, some studies have suggested that the preservation of the orbit is not significantly associated with a higher rate of local recurrence(Carrau, et al. 1999; Wu, et al. 1995). Additionally, some investigations have failed to establish a definite link between orbit preservation and overall survival(Lund, et al. 1998). Particularly in cases involving limited invasion of orbital fat, the choice between tumor resection surgery with orbit exenteration or preservation remains a topic of considerable debate due to the lack of discernible differences(Carrau, et al. 1999; Reyes, et al. 2015; Wang, et al. 2019; Wu, et al. 1995).

1.2. Purpose of Research

The objective of our study was to evaluate the oncological outcomes of sinonasal cancers with orbit invasion from various perspectives, including pathological factors, the extent of orbit invasion, and treatment options.

Chapter 2. Materials and Methods

2.1. Study Objects

This retrospective study was conducted at two tertiary care centers, namely Seoul National University Hospital and Seoul National University Bundang Hospital. The study encompassed a ten-year period, from January 1st, 2009, to December 31st, 2018. The study population consisted of patients who presented with primary sinonasal cancers with orbit involvement at the time of their initial diagnosis. Excluded from the study were patients with a follow-up period of less than 12 months for assessing survival, those with distant metastasis at presentation, individuals in a palliative care context (including those with extensive cavernous sinus involvement, encasement of the internal carotid artery, or extensive infiltration of brain parenchyma), and those with incomplete medical records, including images, surgical reports, or follow-up information. Ultimately, 141 patients met the inclusion criteria and were included as subjects for analysis. A comprehensive review of their medical records, encompassing demographics, pathology, radiological assessment of orbit invasion extent, treatment modalities, survival data, and recurrence outcomes, was conducted.

2.2. Evaluation of orbit invasion

To assess the radiological extent of orbit invasion, we utilized the classification system described by Mario et al. in 2019(Turri-Zanoni, et al. 2019), which is a modified version of the classification originally proposed by Iannetti et al. in 2005(Iannetti, et al. 2005). In Mario's classification, orbit invasion is classified as follows: grade 1 when there is erosion or destruction of the orbital bony wall (Lamina papyracea), grade 2 when there is invasion of the periorbital layer and/or focal invasion of the extraconic periorbital fat, grade 3 when there is invasion of the orbital contents (anterior 2/3 of the orbit), including extra-ocular muscles, optic nerve, ocular bulb, and the skin overlying the eyelids, and grade 4 for involvement of the orbital apex. Illustrative examples of each grade are provided in Figure 1. In our study, grading based on Mario's classification(Turri-Zanoni, et al. 2019) for all study subjects was performed by two expert otorhinolaryngologists.

2.3. Treatment algorithm

The general treatment algorithm for advanced sinonasal malignancies is as follows: First, we conduct a comprehensive assessment of the patient's medical history and imaging in collaboration with the Department of Radiation Oncology and the Department of Hemato-Oncology to determine the appropriateness of initiating neoadjuvant therapy. If the neoadjuvant therapy is not performed, the initial treatment involves surgery, CCRT, RT, or CTx. Subsequently, post-operative RT or CCRT is administered on a case-by-case basis. However, if the neoadjuvant therapy is performed, induction CTx is the initial step. The subsequent course of treatment varies depending on the patient's response. If the cancer response is still in-operable or the patient refuses the operation, CCRT or RT is initiated after induction CTx. Conversely, if the response is stable disease (SD), progressive disease (PD), or partial response (PR) with downstaging, surgical intervention is pursued, with or without orbit exenteration. Post-operative CCRT or RT is also determined on a case-specific basis. The algorithm is depicted in Figure 2, detailing the count of SqCC patients included on a case-by-case basis.

As a result, the definitive treatment approach is primarily divided into two methods: treatments involving orbit exenteration, represented as 'OE' henceforth, and treatments without orbit exenteration, referred to as 'OP' from now on. OE unequivocally refers to surgical procedures with orbit exenteration as the definitive treatment. OP encompasses not only patients who undergo surgical treatment without orbit exenteration as the definitive approach (OP with surgery) but also patients managed with non-operative treatments as the primary strategy, such as CTx or CCRT (OP with other treatments). The induction CTx regimen involves a three-week cycle and includes cisplatin, docetaxel, and fluorouracil. On the other hand, the CCRT regimen consists of conventional standard fractionated RT, delivering a dose of more than 60 Gy, alongside concurrent CTx with weekly administration of cisplatin.

2.4. Analytic method

The definitions and methods employed in our study were as follows. Overall survival (OS) was measured as the time elapsed from the date the patient treatment initiated to the date of their last visit or the date of their demise. Disease-free survival (DFS) was calculated as the time from the date the patient treatment initiated to the date of their last visit without a recurrence of cancer or signs thereof. We utilized the 8th American Joint Committee on Cancer (AJCC) guidelines for cancer staging. Our study primarily focused on the analysis of the relationships between OS, DFS, and factors such as the extent of orbit invasion, T stage, treatment of orbit, induction chemotherapy, and cancer pathology. Specifically, we concentrated on the analysis of SqCC, which was the most prevalent pathology in our study. Survival rates were assessed using the Kaplan–Meier method, and comparisons between survival rates, including OS and DFS, were conducted using the log-rank method (Mantel-Cox). Statistical analysis was performed using SPSS Statistics for Windows, version 22.0 (IBM, Armonk, New York, United States), with statistical significance defined as a p-value less than 0.05.

Our study protocol received approval from the institutional review boards of SNUH and SNUBH and was conducted in accordance with the principles of the Declaration of Helsinki (IRB No. 2210-018-1366).

Chapter 3. Results

3.1. Overall distribution of cancer pathology and orbit invasion grade

In total 141 patients, the average age at diagnosis was 57.3 ± 16.3 years, with 94 males and 47 females. At the time of diagnosis, 52 patients (36.9%) presented with eye symptoms. Thirteen patients underwent orbit exenteration as their definitive treatment. Regarding orbit invasion grade, among 32 patients with grade 1 orbit invasion, only 2 received OE. In the case of 50 patients with grade 2 orbit invasion, 2 patients underwent OE, while in the 38 patients with grade 3 orbit invasion, 5 received OE. Among 21 patients with grade 4 orbit invasion, 4 underwent OE.

Regarding pathology, the distribution was as follows: 68 cases of SqCC (48.2%), 26 cases of adenoid cystic carcinoma (ACC) (18.4%), 14 cases of olfactory neuroblastoma (ONB) (9.9%), 11 cases of lymphoma (7.8%), and 22 cases of other cancers (including 7 sarcomas, 4 adenocarcinomas, 3 Nuclear protein in testis (NUT) midline cancers, 3 neuroendocrine cancers, 2 malignant melanomas, 1 small cell carcinoma, 1 myoepithelial cancer, and 1 verrucous cancer).

Based on Mario's classification for orbit invasion(Turri-Zanoni, et al. 2019), there were 32 patients with grade 1 orbit invasion (22.7%), 50 with grade 2 orbit invasion (35.5%), 38 with grade 3 orbit invasion (27.0%), and 21 with grade 4 orbit invasion (14.9%). When stratified by pathology, among SqCC patients, there were 18 cases with grade 1, 23 with grade 2, 20 with grade 3, and 7 with grade 4 orbit invasions. In ACC patients, there were 5 cases with grade 1, 11 with grade 2, 4 with grade 3, and 6 with grade 4 orbit invasions. In ONB patients, there were 4 cases with grade 1, 7 with grade 2, 3 with grade 3, and no cases with grade 4 orbit invasion. For lymphoma, there were 2 cases with grade 1, 3 with grade 2, 4 with grade 3, and 2 with grade 4 orbit invasion cases (Table 1).

3.2. Survival Outcome in all patients

Out of a total of 141 patients in the study, the 5-year OS rate (5Y OS) was 91.4 ± 2.6%, while the 5-year DFS rate (5Y DFS) was 45.6 ± 4.8%. The Kaplan-Meier curve is depicted in Figure 3. In terms of pathology, there were no significant differences observed in OS according to the results of the Log Rank (Mantel-Cox) test. However, in the case of DFS, significant differences were noted based on pathology, as outlined in Table 2. From pairwise comparisons, patients with SqCC showed a significantly lower DFS rate (5Y 35.1±7.2%) than lymphoma (5Y 90.9 ± 8.7) and ONB (5Y 80.8 ± 12.2) (Table 3). Additionally, patients with ACC also showed significantly lower DFS rate (5Y 53.8 ± 10.3) than ONB. However, there were no significant difference observed in DFS between SqCC and ACC or between ONB and lymphoma.

3.3. Survival Outcome of SqCC patients by T stage and orbit invasion grade

When analyzing 68 patients with SqCC, significant differences were observed in both overall survival (OS) and disease-free survival (DFS) in relation to T staging (T3, T4a, T4b) (Table 4). On the other hand, according to orbit invasion grade, there were no significant differences observed in either OS or DFS (Table 5, Figure 4).

3.4. Survival Outcome of SqCC patients by treatments

In order to focus on the most common pathology and exclude other factors that could potentially influence the assessment of treatment outcomes, we analyzed the treatment outcomes in 68 patients with SqCC. Within this group, we assessed the prognosis of these 68 SqCC patients according to three distinct types of definitive treatment: OE, OP with surgery, and OP with other treatments (including RT, CTx, and CCRT). Out of these patients, 8 underwent OE, 24 received OP with surgery, and 36 were treated with OP with other treatments. Importantly, the patients were found to be evenly distributed among these different definitive treatment categories based on orbit grade and T stage, ensuring a balanced representation within each treatment group (Table 6,7).

In terms of OS among SqCC patients, no significant differences were observed between surgical and non-surgical definitive treatments. There were also no significant differences among the three different definitive treatments. However, for DFS, there were notable differences between surgical and non-surgical definitive treatments and between OE, OP with surgery, and OP with other treatments (Table 8, Figure 5). Notably, patients who underwent OP with surgery exhibited a significantly longer DFS compared to those received OP with other treatments (Table 9).

We further conducted an analysis focusing on SqCC patients with orbit invasion grades 1, 2 and 3, excluding only the severe cases (grade 4). Within this subgroup of SqCC patients, the distribution of treatments consisted of 7 patients undergoing OE (5Y OS 100, 5Y DFS 60.0 ± 21.9), 22 patients treated with OP with surgery (5Y OS 100, 5Y DFS 51.8 ± 15.3), and 32 patients treated with OP with other treatments (5Y OS 79.8 ± 8.2, 5Y DFS 23.0 ± 8.3). For OS rates, no significant differences were observed among these three groups (overall comparisons Chi-square 5.296, p-value 0.071). However, significant differences were noted in DFS rates among the three groups (overall comparisons Chi-square 6.725, p-value 0.035). From pairwise comparisons, patients treated with OP with surgery had a significantly improved DFS rate compared to those treated with OP with other treatments (Chi-square 4.961, p-value 0.026). However, no significant differences were observed in pairwise comparisons between other definitive treatment categories. Additionally, we performed an analysis on SqCC patients with orbit invasion grades 2, 3, and 4, excluding only the mild cases (grade 1). Within this subset, 6 patients received OE (5Y OS 100, 5Y DFS 40.0 ± 21.9), 16 patients were treated with OP with surgery (5Y OS 93.3 ± 6.4, 5Y DFS 65.8 ± 15.0), and 28 patients were treated with OP with other treatments (5Y OS 85.5 ± 8.0, 5Y DFS 18.0 ± 8.0). From analysis, same results were found. No significant differences were observed in OS rates among these three groups (overall comparisons Chi−square 1.236, p−value 0.539) and significant differences were noted in DFS rates (overall comparisons Chi−square 8.149, p−value 0.017). Also, patients treated with OP with surgery had a significantly improved DFS rate compared to those treated with OP with other treatments (Chi−square 7.280, p−value 0.007) and no significant differences were observed between other definitive treatment categories from pairwise comparisons.

Finally, we analyzed about the SqCC patients who treated with induction CTx. In this subgroup analysis, patients were categorized into three groups. The first group included patients whose response was PR and subsequently underwent surgery (comprising both OE and OP with surgery) as the definitive treatment (11 patients). The second group consisted of patients with an SD or PD response who also underwent surgery as the definitive treatment (6 patients). The third group comprised patients with an SD or PD response who were treated with RT, CCRT or CTx (OP with other treatments) as their definitive treatment (20 patients). There were no significant differences in OS rates. However, from DFS rates, patients with an SD or PD response and subsequently underwent nonsurgical treatments had significantly lower DFS rates than others (Table 10, 11).

Chapter 4. Discussion

In this study, we conducted an analysis of OS and DFS among 141 patients with sinonasal cancer featuring orbit invasion, considering various characteristics. The 5Y OS was 91.4 ± 2.6% and 5Y DFS was 45.6 ± 4.8% in entire subjects of different pathologies. SqCC constituted the majority (48.2%) of pathologies. Our findings revealed that there were no significant differences in OS rates among the different pathological types of sinonasal cancer. However, it is noteworthy that SqCC and ACC tended to exhibit shorter DFS compared to other pathological types.

Within the SqCC group, both OS and DFS showed significant differences based on the T stage, which is a common trend observed in many cancer types. In contrast, OS and DFS did not significantly differ when considering the orbit invasion grade proposed by Mario(Turri-Zanoni, et al. 2019). In a specific analysis focusing on SqCC cases, it was observed that when tumor resection with orbit preservation (OP with surgery) was chosen as the definitive treatment, DFS was significantly extended compared to cases where surgery was not the chosen definitive treatment (OP with other treatments). Furthermore, no significant difference in DFS was found between those who underwent orbit exenteration as the definitive treatment (OE) and those who underwent OP with surgery. Therefore, given the absence of a significant difference in OS among OE, OP with surgery, and OP with other treatments, we inferred that OP with surgery might be the ideal definitive treatment option where applicable. This inference is grounded in the fact that OP with surgery contributes to an extended DFS while ensuring survival in SqCC cases with orbit invasion. The analysis of subgroups excluding mild or severe orbit invading patients (grade 1, 2, and 3 cases or 2, 3, and 4 cases) both showed the same results. From the results about the induction CTx, surgical definitive treatments showed longer DFS than non-surgical definitive treatments.

Regarding differences in OS and DFS rates based on the extent of orbit invasion, there have been conflicting findings in the literature. Some studies have reported no significant differences in OS, disease-specific survival (DSS), and progression-free survival (PFS) rates in sinonasal cancers according to the extent of orbit invasion, which aligns with our results(Shin, et al. 2022). However, other studies have indicated that OS and DFS rates do vary significantly depending on orbit invasion grades(Turri-Zanoni, et al. 2019). Additionally, one study investigated the pre-treatment assessment of local extension in sinonasal cancer(Salfrant, et al. 2021). This study evaluated the diagnostic performance of CT and MRI in assessing local invasion by comparing them to histopathological data. It found that the signs of orbital invasion had a low predictive positive value. This could potentially elucidate the varying outcomes regarding the relationship between the extent of orbit invasion and the prognosis of sinonasal cancer. Due to the imperfect diagnostic accuracy of imaging methods, diverse results can arise. In terms of T staging, some studies, including ours, have shown significant differences in OS or DFS between T stages(Turri-Zanoni, et al. 2019). The main difference of our study was that we limited the comparison within the subset of SqCC patients. Although orbit invasion is one of the important prognosis factors in sinonasal cancer, our findings suggest that predicting the prognosis of the cancer solely based on orbit invasion may not be sufficient. This is likely because sinonasal cancer can also invade other nearby structures, such as the dura, skull base, skin, and more. Therefore, we recommend that treatment decisions should always consider the overall extent of invasion by the cancer.

Several studies have reported varying results regarding the comparison between orbit exenteration and tumor resection with orbit preservation, which are in line with our findings regarding OS and DFS rates in SqCC patients(Lisan, et al. 2016; Shin, et al. 2022). However, there is also a study indicating significantly lower OS and

DFS rates in the orbit exenteration group compared to the orbit preservation group, particularly in patients with invasion of the anterior 2/3 of the orbit(Turri-Zanoni, et al. 2019). This issue remains highly controversial because another study about the patients with invasion beyond the orbital periosteum involving orbital soft tissues showed a higher OS rate in the orbit exenteration group than in the orbit preservation group(Safi, et al. 2017). However, the two previous studies(Turri-Zanoni, et al. 2019), (Safi, et al. 2017) did not specifically focus on a particular pathology but instead included sinonasal cancer cases with various underlying pathologies. Additionally, in cases where orbit preservation treatments were compared to orbit exenteration outcomes, the orbit preservation treatments encompassed both surgical and nonsurgical approaches, such as CCRT, as the definitive treatment(Turri-Zanoni, et al. 2019), (Safi, et al. 2017). In the context of SqCC, some studies have reported that orbit preservation, whether through surgical or non-surgical means, is not significantly associated with higher local recurrence rates(Carrau, et al. 1999; Wu, et al. 1995) or overall survival rates(Lund, et al. 1998). Notably, a recent meta-analysis on orbit preservation in sinonasal cancer indicated a slight inclination toward orbit preservation in SqCC cases for better outcome, although the difference was not statistically significant(Reyes, et al. 2015). Our study offers significant strengths compared to these previous studies. One key aspect is our division of orbit-preserving definitive treatments into surgical and non-surgical categories. Additionally, our study's focus on treatment analysis for a single pathology (SqCC) is another strength, as there were differences in prognosis based on pathology. Furthermore, our study benefits from a large sample size, encompassing 141 sinonasal cancer cases with orbit invasion and 68 SqCC cases, all from two tertiary centers, which are connected.

Despite the ongoing controversies surrounding this issue, we would like to recommend surgical treatment as the preferred definitive approach for sinonasal cancer with orbit invasion, particularly in cases with SqCC, when feasible. Recently there have been some studies including the results about the effectiveness of induction CTx in advanced SqCC of sinonasal cancers(Ock, et al. 2016). Further, our study' s result showed the better outcome of surgical definitive treatments compared to non-surgical definitive treatments when both treated after induction CTx. Moreover, we recommend that the surgical approach prioritize tumor resection with orbit preservation over orbit exenteration. Over the past few decades, there has been a tendency to recommend and perform orbit exenteration as the extent of orbit invasion widens. However, as outlined in our study protocol, the utilization of induction CTx and adjuvant therapies, including post-operative RT, CTx, or CCRT, appears to render tumor resection with orbit preservation a more viable option when surgery is feasible as the definitive treatment. In essence, induction CTx and adjuvant therapies play a pivotal role in preserving the orbit. Based on our findings and our collective experiences, we propose initiating induction chemotherapy as the first-line treatment, if possible, for patients with grade 2, 3, or 4 orbit invasions in sinonasal cancer. Subsequently, if there is evidence of treatment response, tumor resection with orbit preservation should be considered as the primary surgical approach, if feasible. However, if the disease progresses, orbit exenteration may be contemplated as a last resort.

Our study has several limitations. One of the limitations we want to mention is the results about subgroup analysis about SqCC patients with orbit invasion grade 2 and 3, which excluded both severe (grade 4) and mild (grade 1) cases. From 43 SqCC patients with orbit invasion grade 2 and 3, the distribution of treatments consisted of 5 patients undergoing OE (5Y OS 100, 5Y DFS 50.0 ± 25.0), 14 patients treated with OP with surgery (5Y OS 100, 5Y DFS 61.5 ± 16.6), and 24 patients treated with OP with other treatments (5Y OS 83.5 ± 9.0, 5Y DFS 20.1 ± 8.9). There were no significant differences between three treatments in both OS (overall comparisons Chi-square 2.942, p-value 0.230) and DFS rates (overall comparisons Chi-square 5.473, p-value 0.065). This is different results contrast to analysis about DFS rates in all SqCC patients or grade 1,2,3 or grade 2,3,4 orbit invasion SqCC patients. In other words, for ambiguous cases (grade 2 and 3), which always make the physicians concern about the definite treatments, no significantly better treatment showed up between three definite treatments. Further analysis and research about grade 2 and 3 orbit invasion SqCC will be needed.

There are also other limitations. Firstly, it is a two-center study that included only Korean patients. Further research incorporating multiple centers and a more ethnically diverse patient population is warranted. Secondly, the relatively small number of patients and the uneven distribution of patients among non-SqCC subgroups may have influenced the results of our analysis about 141 patients. Additionally, because our study was retrospective in nature, the included patients may not be fully representative of each subgroup. Also, the grading of orbit invasion was conducted by two expert otorhinolaryngologists. While both experts were highly skilled in interpreting rhinology-related images, the grading process may have introduced some degree of subjectivity.

Chapter 5. Conclusion

Orbit invasion grading based on imaging failed to reflect the prognosis of the sinonasal cancer with orbit invasion. When surgical treatment was possible, it consistently demonstrated better survival outcomes for sinonasal SqCC with orbit invasion compared to non-surgical treatment. Among surgical approaches, both tumor resection with orbit preservation and orbit exenteration yielded similar survival outcomes, regardless of the orbit invasion grade.

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Table 1. Distribution of orbit invasion by sinonasal malignancy pathology

	SqCC	ACC	ONB	Lymphoma	Others	Total
Gr 1	18	5	4	2	3	32
Gr 2	23	11	7	3	6	50
Gr 3	20	4	3	4	7	38
Gr 4	7	6	0	2	6	21
Total	68	26	14	11	22	141

Gr, Grade; SqCC, Squamous cell carcinoma; ACC, Adenoid cystic carcinoma; ONB, Olfactory neuroblastoma

Table 2. Overall comparison results of Log Rank (Manel−Cox) test for overall survival and disease−free survival by sinonasal malignancy pathology

	5Y OS (%)	5Y DFS (%)
SqCC (68)	89.0 ± 4.3	35.1 ± 7.2
ACC (26)	96.0 ± 3.9	53.8 ± 10.3
ONB (14)	100	80.8 ± 12.2
Lymphoma (11)	100	90.9 ± 8.7
Others (22)	83.1 ± 9.1	18.2 ± 9.8
Overall comparisons Chi−Square (p−value)	3.571 (0.467)	18.748 (0.001*)

SqCC, Squamous cell carcinoma; ACC, Adenoid cystic carcinoma; ONB, Olfactory neuroblastoma; 5Y, 5−year; OS, overall survival; DFS, disease−free survival

Table 3. Pairwise comparison result of Log Rank (Manel−Cox) test for disease−free survival by sinonasal malignancy pathology

	SqCC		ACC		ONB		Lymphoma		Others	
Log−Rank	Chi−Square	p−value	Chi−Square	p−value	Chi−Square	p−value	Chi−Square	p−value	Chi−Square	p−value
SqCC			0.664	0.415	7.677	0.006*	6.327	0.012*	2.936	0.087
ACC	0.664	0.415			4.666	0.031*	3.305	0.069	3.067	0.080
ONB	7.677	0.006*	4.666	0.031*			0.217	0.641	12.034	0.001*
Lymphoma	6.327	0.012*	3.305	0.069	0.217	0.641			10.065	0.002*
Others	2.936	0.087	3.067	0.080	12.034	0.001*	10.065	0.002*		

SqCC, Squamous cell carcinoma; ACC, Adenoid cystic carcinoma; ONB, Olfactory neuroblastoma

Table 4. Overall comparison results of Log Rank (Manel-Cox) test for overall survival and disease-free survival by T staging in squamous cell carcinoma patients

	5Y OS (%)	5Y DFS (%)
T3 (19)	100	53.1 ± 15.5
T4a (31)	91.9 ± 5.6	38.6 ± 10.2
T4b (18)	72.7 ± 11.7	10.4 ± 9.4
Overall comparisons Chi-Square (p-value)	6.172 (0.046*)	9.98 (0.007*)

5Y, 5-year; OS, overall survival; DFS, disease-free survival

Table 5. Overall comparison results of Log Rank (Manel−Cox) test for overall survival and disease−free survival by orbit invasion grades in squamous cell carcinoma patients

	5Y OS (%)	5Y DFS (%)
Gr 1 (18)	85.9 ± 9.3	44.6 ± 14.0
Gr 2 (23)	94.1 ± 5.7	39.3 ± 11.4
Gr 3 (20)	88.2 ± 8.0	27.9 ± 12.8
Gr 4 (7)	80.0 ± 17.9	26.8 ± 21.4
Overall comparisons Chi−Square (p−value)	1.154 (0.764)	2.075 (0.557)

Gr, Grade; 5Y, 5−year; OS, overall survival; DFS, disease−free survival

Table 6. Distribution of SqCC patients' orbit invasion grade by definitive treatment

	Grade 1	Grade 2	Grade 3	Grade 4	Total
OP, other Tx	8 (22.2%)	14 (38.9%)	10 (27.8%)	4 (11.1%)	36 (100%)
OP, surgery	8 (33.3%)	8 (33.3%)	6 (25.0%)	2 (8.3%)	24 (100%)
OE	2 (25.0%)	1 (12.5%)	4 (50.0%)	1 (12.5%)	8 (100%)
Total	18 (26.5%)	23 (33.8%)	20 (29.4%)	7 (10.3%)	68 (100%)

From Fisher's exact test, there was no significant relationship between orbit grade and the choice of treatments (p−value = 0.729).

OE, patients treated with treatments including orbit exenteration as definitive treatment; OP, surgery, patients treated by surgical treatments without orbit exenteration as definitive treatment; OP, other Tx, patients treated by non−surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment

Table 7. Distribution of SqCC patients' T stage by definitive treatment

	T stage 3	T stage 4a	T stage 4b	Total
OP, other Tx	10 (27.8%)	14 (38.9%)	12 (33.3%)	36 (100%)
OP, surgery	8 (33.3%)	12 (50.0%)	4 (16.7%)	24 (100%)
OE	1 (12.5%)	5 (62.5%)	2 (25.0%)	8 (100%)
Total	19 (27.9%)	31 (45.6%)	18 (26.5%)	68 (100%)

From Fisher's exact test, there was no significant relationship between T stage and the choice of treatments (p−value = 0.515). OE, patients treated with treatments including orbit exenteration as definitive treatment; OP, surgery, patients treated by surgical treatments without orbit exenteration as definitive treatment; OP, other Tx, patients treated by non−surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment

Table 8. Overall comparison results of Log Rank (Manel-Cox) test for overall survival and disease-free survival by orbit treatment in SqCC patients

<table>
<tr><th></th><th colspan="2">5Y OS (%)</th><th colspan="2">5Y DFS (%)</th></tr>
<tr><td>OE (8)</td><td rowspan="2">96.6 ± 3.4</td><td>100</td><td rowspan="2">53.9 ± 7.6</td><td>50.0 ± 20.4</td></tr>
<tr><td>OP, surgery (24)</td><td>95.7 ± 4.3</td><td>56.0 ± 14.1</td></tr>
<tr><td>OP, other Tx (36)</td><td>81.5 ± 7.6</td><td>81.5 ± 7.6</td><td>21.1 ± 7.7</td><td>21.1 ± 7.7</td></tr>
<tr><td>Overall comparisons
Chi-Square
(p-value)</td><td>2.955
(0.086)</td><td>3.053
(0.217)</td><td>9.057
(0.003*)</td><td>9.071
(0.011*)</td></tr>
</table>

OE, patients treated with treatments including orbit exenteration as definitive treatment; OP, surgery, patients treated by surgical treatments without orbit exenteration as definitive treatment; OP, other Tx, patients treated by non-surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment; 5Y, 5-year; OS, overall survival; DFS, disease-free survival

Table 9. Pairwise comparison result of Log Rank (Manel-Cox) test for disease-free survival by orbit treatments in SqCC patients

	OP, other Tx		OP, surgery		OE	
Log-Rank	Chi-Square	p-value	Chi-Square	p-value	Chi-Square	p-value
OP, other Tx			7.556	0.006*	2.880	0.090
OP, surgery	7.556	0.006*			0.062	0.803
OE	2.880	0.090	0.062	0.803		

OE, patients treated with treatments including orbit exenteration as definitive treatment; OP, surgery, patients treated by surgical treatments without orbit exenteration as definitive treatment; OP, other Tx, patients treated by non-surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment

Table 10. Overall comparison results of Log Rank (Manel-Cox) test for overall survival and disease-free survival by induction CTx response and subsequent treatments in SqCC patients who treated with induction CTx

	3Y OS (%)	3Y DFS (%)
PR (+), surgery (11)	100	50.9 ± 16.3
SD/PD, surgery (6)	100	55.6 ± 24.8
SD/PD, other Tx (20)	71.3 ± 12.6	18.3 ± 9.5
Overall comparisons Chi-Square (p-value)	5.002 (0.082)	11.081 (0.004*)

SqCC, Squamous cell carcinoma; CTx, chemotherapy; PR, partial response; SD, stable disease; PD, progressive disease; other Tx, patients treated by non-surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment; 3Y, 3-year; OS, overall survival; DFS, disease-free survival

Table 11. Pairwise comparison result of Log Rank (Manel−Cox) test for disease−free survival by induction CTx response and subsequent treatments in SqCC patients who treated with induction CTx

	PR (+), surgery		SD/PD, surgery		SD/PD, other Tx	
Log−Rank	Chi−Square	p−value	Chi−Square	p−value	Chi−Square	p−value
PR (+), surgery			0.057	0.811	7.890	0.005*
SD/PD, surgery	0.057	0.811			5.091	0.024*
SD/PD, other Tx	7.890	0.005*	5.091	0.024*		

SqCC, Squamous cell carcinoma; CTx, chemotherapy; PR, partial response; SD, stable disease; PD, progressive disease; other Tx, patients treated by non−surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment; OS, overall survival; DFS, disease−free survival

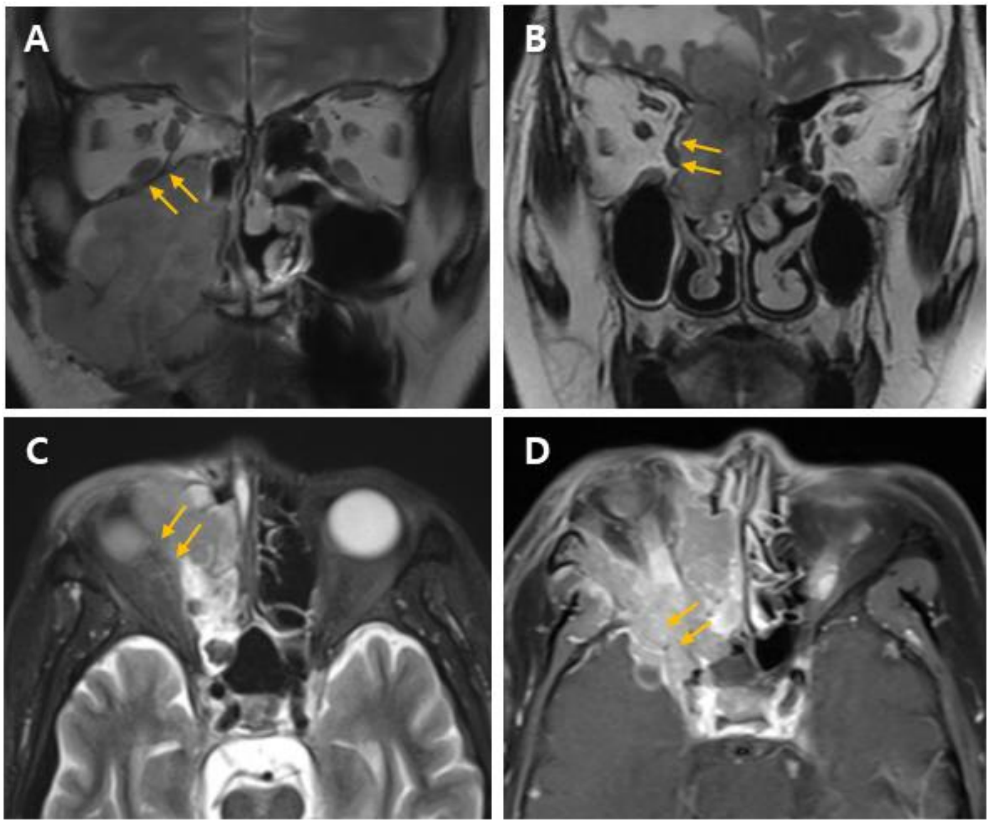

Figure 1. Examples of 4 grades of orbit invasion

A : Orbit invasion grade 1. There is an erosion of right inferior orbital bony wall erosion.
B : Orbit invasion grade 2. There is an invasion of the periorbital layer and focal invasion of the extraconic periorbital fat.
C : Orbit invasion grade 3. There is an invasion of the orbital contents at the anterior 2/3 of the orbit, including extra−ocular muscles, optic nerve, and ocular bulb.
D : Orbit invasion grade 4. There is an involvement of the orbital apex.

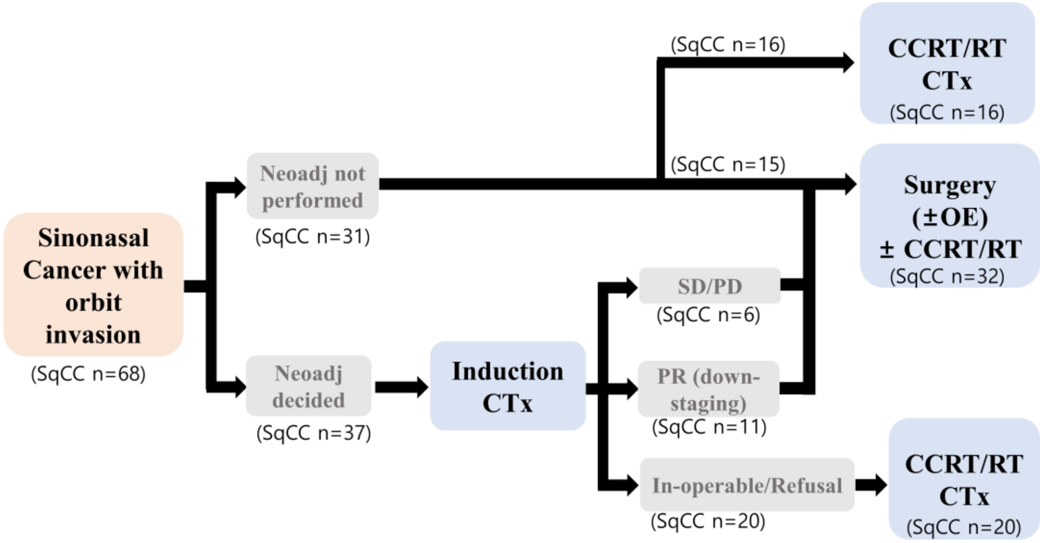

Figure 2 Treatment algorithm for the advanced sinonasal malignancy

If the neoadj is not performed, initial treatment includes operation, RT or CCRT, and CTx. Operations can be followed by post-operative RT or CCRT on a case-by-case basis. If neoadjuvant therapy is deemed appropriate, induction CTx is the initial step. If the response is in-operable or the patient refuses the operation, CCRT or RT is administered afterwards. In cases of SD, PD, or PR with downstaging, surgical intervention is considered, with or without post-operative CCRT or RT. A total of 68 SqCC patients were classified and depicted according to this treatment algorithm in this figure.
SqCC, Squamous cell carcinoma; neoadj, neoadjuvant therapy; CTx, chemotherapy; OE, orbit exenteration; CCRT, concurrent chemo-radiotherapy; RT, radiotherapy; SD, stable disease; PD, progressive disease; PR, partial response

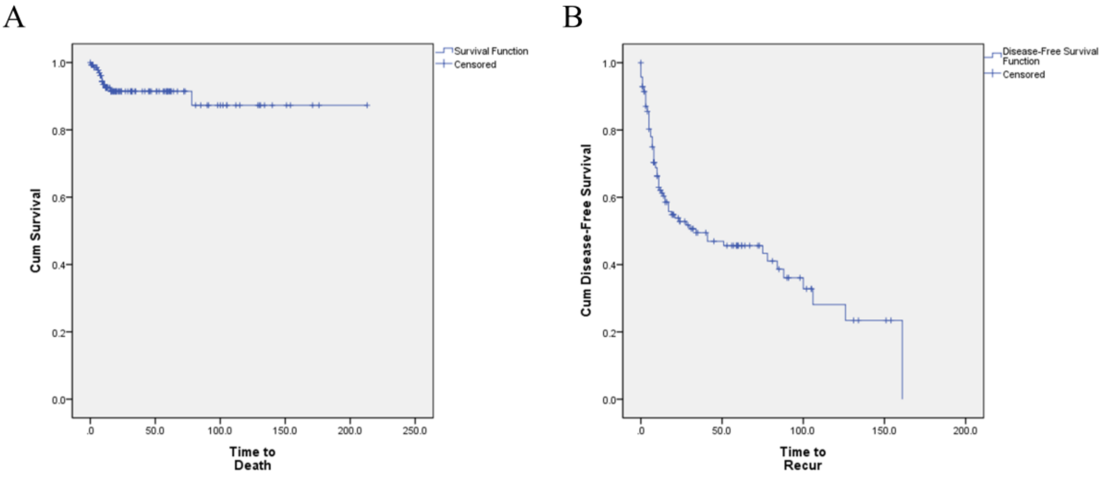

Figure 3. The Kaplan–Meier curve of overall survival and disease–free survival in 141 patients diagnosed with sinonasal malignancy with orbit invasion

A : The Kaplan–Meier curve of overall survival in 141 patients diagnosed with sinonasal malignancy with orbit invasion.
B : The Kaplan–Meier curve of disease–free survival in 141 patients diagnosed with sinonasal malignancy with orbit invasion.
Cum: cumulative; The unit of axis X is days.

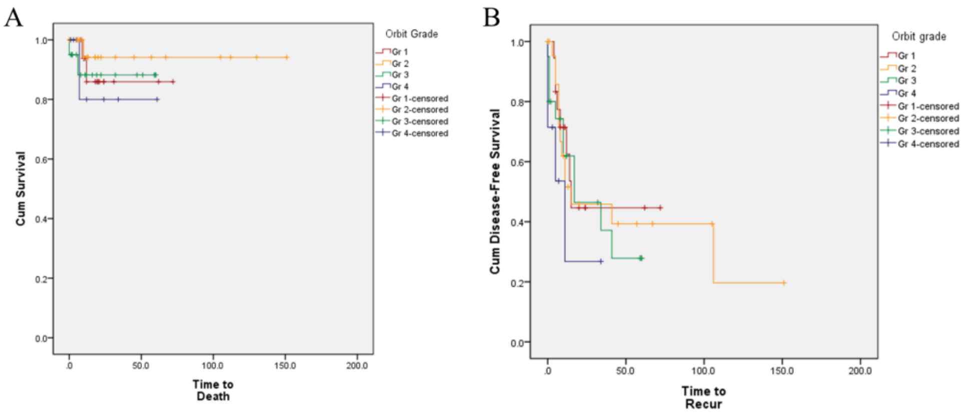

Figure 4. The Kaplan–Meier curve of overall survival and disease–free survival in SqCC patients, described by the orbit invasion grades.

A : The Kaplan–Meier curve of overall survival in 68 patients with SqCC, depicted according to orbit grade.
B : The Kaplan–Meier curve of disease–free survival in 68 patients with SqCC, depicted according to orbit grade.
Gr: Grade; Cum: cumulative; The unit of axis X is days.

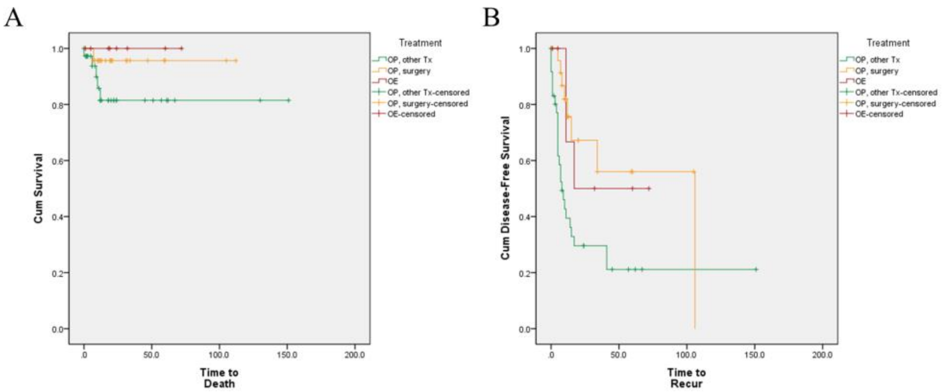

Figure 5. The Kaplan−Meier curve of overall survival and disease−free survival in SqCC patients, described by definitive treatments

A : The Kaplan−Meier curve of overall survival in 68 patients with SqCC, depicted according to definitive treatments
B : The Kaplan−Meier curve of disease−free survival in 68 patients with SqCC, depicted according to definitive treatments
OE, patients treated with treatments including orbit exenteration as definitive treatment; OP, surgery, patients treated by surgical treatments without orbit exenteration as definitive treatment; OP, other Tx, patients treated by non−surgical treatments such as chemotherapy or concurrent chemoradiotherapy as definitive treatment; Cum: cumulative; The unit of axis X is days.

국문초록

비부비동암은 종종 안와를 침범한다. 안와를 침범하는 비부비동암의 치료 방침은 치료자, 의료기관 및 침범의 정도에 따라 다양할 수 있다. 안와를 보존할지 여부에 따라 구체적인 치료 전략은 경우에 따라 다양하며 질병의 예후 결과에도 영향을 미친다. 현재 비부비동암에는 수술, 항암치료, 방사선치료 또는 동시항암화학방사선치료를 포함한 다중복합치료 접근법이 자주 사용된다. 이번 연구는 안와 침범 비부비동암의 치료적 측면에 있어서 임상적 특징을 평가해보고자 했다.
2009년부터 2018년까지 서울대학교병원에서 치료받은 안와를 침범하는 원발성 비부비동암 환자들을 대상으로 후향적 연구를 실시했다. 병리적인 암의 종류, 안와 침범 정도, 치료전략, 재발률 및 생존률과 같은 요인들을 조사했다.
141명의 안와 침범 비부비동암 환자 중 가장 흔한 암의 종류는 편평상피세포암(68명, 48.2%)이었다. 편평상피세포암 환자는 다른 암의 종류에 비해 유의미게 낮은 질환 생존율 (5년 생존율 35.1±7.2%)을 보였다. 안와 침범 정도에 따라 전체생존율 및 무병생존율은 유의하게 다르지 않았다. 그러나 편평상피세포암 환자들만의 분석에서 안와를 보존하는 종양절제술이 주치료로 수행될 때 수술이 주치료로 수행되지 않은 경우보다 무병생존율이 유의하게 길었다. 주치료로 안와절제술을 받은 환자와 주치료로 안와를 보존하는 종양절제술을 받은 환자 간에는 무병생존율에 유의한 차이가 없었다.
안와를 보존하는 종양절제술은 비부비동 편평상피세포암의 안와 침범 사례에서 장기적인 무병생존율를 보장하면서 전체생존율을 확보하기에, 선호될만한 주치료로 보인다. 또한 안와 침범 정도가 증가할수록 주치료로 안와를 보존하는 종양 절제술을 시행하고, 안와 침범 정도가 감소할수록 주지료로 항암치료나 방사선치료를 선택하는 것이 비부비동암에 대한 더 유리한 접근법일 수 있겠다.

주요어 : 비부비동암, 안와, 생존 분석, 사망률, 무병생존율

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