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Treatment for SMARCB1 (INI-1) deficient sinonasal tumor: a single-institution study

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Currently, less than 200 cases of SMARCB1-deficient sinus cancer (SDSC) have been documented. Little information is available about the best treatment options or prognosis for SDSC. From September 2016 to November 2022, the medical records of 22 people with SDSC were evaluated retrospectively. Patient demographics, staging, pathology findings, treatment details, recurrence, metastasis, and survival outcomes were all investigated by the researchers. The 1-, 2-, and 3-year overall survival (OS) rates for the entire cohort were 89.8%, 84.2%, and 45.1%, respectively, as were the 1-, 2-, and 3-year progression-free survival (PFS) rates of 81.8%, 63.8%, and 31.9%. After induction chemotherapy, 66.7% (10/15) of patients exhibited decreased tumor volume. Patients who accepted chemoradiotherapy had a better 2-year OS (100% vs. 72.7%, p=0.048) than those who accepted surgery as a preference. However, there is no difference in 2-year PFS between the two groups (53.0% vs. 75.8%, p=0.59). Patients with progressed or stable disease after induction chemotherapy had a higher risk of developing local recurrence (p=0.007); they also showed poor 2-year PFS (40.0% vs. 82.1%, p=0.019). SDSC had a poor 3-year OS, with a PFS of less than 50%. For locally advanced SDSC, chemoradiotherapy might be managed before surgery, especially in patients who benefit from induction chemotherapy.

Key words: SMARCB1-deficient sinonasal carcinoma; prognosis; induction chemotherapy; chemoradiotherapy; surgery

Sinonasal undifferentiated carcinoma (SNUC) was proposed in the 1980s and was defined as an undifferentiated carcinoma of the sinonasal tract without glandular and squamous features and not otherwise classifications. With recent breakthroughs in molecular and immunohistochemical techniques, more and more unique molecular abnormalities were identified [1]. In 2014, Agaimy et al. [2] and Bishop et al. [3] independently described the loss of nuclear SMARCB1 expression in some SNUCs. Since then, SMARCB1-deficient sinonasal carcinoma represents an emerging poorly differentiated/undifferentiated sinonasal carcinoma. Histologically, the tumors had in common cellular monotony with relatively monomorphic small-to-medium-sized rounded nuclei with dispersed chromatin, variably prominent nucleoli, and indistinctive cytoplasmic borders [4]. Immunohistochemistry showed consistent expression of pan-cytokeratin and loss of SMARCB1 (INI1) expression [4]. Some cases present the features of nonkeratinizing squamous cell carcinoma composed of cohesive clusters and sheets of oval to polygonal cells with indistinct cell borders present within a background of necrotic debris [5]. Less than 200 cases have been reported to date. Although some novel insights have propelled the discovery of numerous potential therapeutic vulnerabilities of SMARCB1-deficient cancers. The treatment modality consensus is not well established. The value of chemotherapy, especially induction chemotherapy, is still unknown. It is necessary to determine the consequences of surgery, chemotherapy, and radiotherapy for better treatment outcomes. In this study, we aimed to investigate the prognosis of SMARCB1-deficient sinonasal carcinoma (SDSC), evaluate induction chemotherapy's value, and discuss the optimal treatment mode.

Patients and methods

Patients. Twenty-six consecutive patients with primary INI-1 deficient sinonasal carcinoma diagnosed at the Eye & ENT Hospital, Fudan University, from September 2016

to November 2022, were retrospectively reviewed and staged according to the 8th edition of TNM (tumor, node, metastasis) AJCC (American Joint Committee on Cancer). Four patients were excluded from accepting chemoradiotherapy at other hospitals. None of the patients had proof of distant metastasis at the initial diagnosis. Data collection was conducted, including the patient's medical histories, baseline characteristics, image findings, treatment modalities, and follow-up visit information. The diagnosis of SDSC was made by two pathologists at our hospital, using morphologic features and immunohistochemical analysis in all cases. The study and data collection were carried out with approval from the Research Ethics Committee of Eye & ENT Hospital, Fudan University (No. 2021181), and informed consent for the research was obtained from the patients. This study adherence to the Declaration of Helsinki.

Treatment. The primary treatment regimens were determined by tumor stage and the preference of patients. Combined surgery with chemoradiotherapy was the primary principle. Surgery was preferred for patients whose lesions could be completely removed; if else, induction chemotherapy (IC) was used to reduce the tumor burden.

The protocols of IC were TPF/TP (docetaxel+cisplatin±fluorouracil), GP (gemcitabine+cisplatin), or EP (etoposide+cisplatin). Cisplatin was administered as concurrent therapy at a dose of 75 mg/m^2 every three weeks, with nedaplatin as an alternative. All radiation treatments were delivered using intensity-modulated radiation therapy (IMRT) or volumetric intensity-modulated arc therapy (VMAT). The average prescribed dose for the primary tumor was 66–70 Gy of 2.0–2.20 Gy/fractions (5 fractions per week) and 60–62 Gy of 2.0 Gy/fractions for complete resection.

Endoscopic endonasal surgery was performed for patients who underwent resection. The resection margins were classified as complete tumor resection (R0), microscopic residual disease (R1), and gross residual disease (R2). Skull base reconstruction was managed for large defects of the anterior cranial base.

Evaluation of response to IC. All the patients accepted MRI and/or CT scans of the head and neck before and after IC to evaluate the tumor response to chemotherapy. MRI and/or CT images were loaded into the uRT-TPOIS treatment planning system (uRT-linac 506c, United-imaging, China). Two senior radiation oncologists contoured the tumor and calculated the tumor volume.

Due to the irregular growth of the sinonasal tumors, the maximum diameter measurement does not reflect the size of the tumor well. We calculated the tumor volume to comprehensively evaluate the size of the mass. Referring to the WHO's (World Health Organization) evaluation criteria in solid tumors, PR was defined as tumor volume decreasing more than 50%, PD as tumor volume increasing more than 25%, SD with tumor volume decreasing less than 50% and without new lesions compared with baseline. Orbital involvement referred to the criterion: grade I with erosion or destruction of the orbital wall, grade II with the invasion of extraconal orbital fat, and grade III with the invasion of extraocular muscles, optic nerve, globe, or eyelid skin [6].

Statistical analysis. Descriptive statistics were used to compare baseline characteristics. Kaplan-Meier analysis was used to determine the overall survival (OS) and progression-free survival (PFS) rates. The log-rank test was used to compare survival curves. Categorical variables were compared using Fisher's exact test. Two-tailed $p<0.05$ was statistically significant for tests. R (version 4.2.0) was used for all analyses.

Table 1. Patient characteristics (n=22).

Characteristics	No. of patients	%
Age (years)		
<60	14	63.6
≥60	8	36.4
Sex		
Male	15	68.2
Female	7	31.8
Smoking status		
Never	15	68.2
Active/Former	7	31.8
Tumor invasion		
T3	1	4.5
T4a	9	40.9
T4b	12	54.5
Nodal status		
N negative	18	81.8
N positive	4	18.2
Clinical Stage		
Stage III	1	4.5
Stage IVa	7	31.8
Stage IVb	14	63.6
Treatment		
Surgery+Chemoradiotherapy	10	45.5
Chemotherapy+Surgery	1	4.5
Chemoradiotherapy+Surgery	7	31.8
Chemoradiotherapy	4	18.2
Radiation technique		
IMRT	13	59.1
VMAT	8	36.4
Induction chemotherapy mode		
GP	2	9.1
EP	4	18.2
TPF	5	22.7
TP	4	18.2

Results

Patient characteristics. The clinicopathological features are summarized in Table 1. There were 15 males and seven females in the group, with a median age of 55 (ranging from 29 to 73). T4 disease was presented in 21 of 22 patients

(95.5%) in this cohort, while brain invasion was presented in 13 patients (59.1%). Nineteen patients (86.4%) had orbital invasion, with 8 having grade II and 9 having grade III. Seventeen (77.3%) tumors originated from the ethmoid sinuses, one (4.5%) from the sphenoid sinuses, and four (18.2%) from the frontal sinuses. Four cases (18.2%) showed cervical node metastases at diagnosis. Surgery with adjuvant chemoradiotherapy (45.5%), definitive chemoradiotherapy (18.2%), or chemoradiotherapy followed by surgery (31.8%) were used as treatments, and one case with IC combined with surgery. Fifteen of these patients (68.2%) with measurable lesions were treated with induction chemotherapy, including GP (2), EP (2), TPF (5), and TP (4). 11 patients performed surgery as preferred treatment, while 11 patients underwent chemoradiotherapy first. Except for one case with uncontrolled after surgery, 13 patients (59.1%) were delivered with IMRT and 8 (36.4%) with VMAT.

The efficacy of chemoradiotherapy. Among all 15 patients accepting IC, five (33.3%) had increasing tumor volume, while ten (66.7%) had decreasing tumor volume (Figure 1). PD occurred in 1 of 4 patients treated with GP, 1 of 2 with EP, 2 of 5 with TPF, and 1 of 4 with TP. Figure 2 summarizes the tumor reaction to different IC modes.

Radiation was provided to 21 patients, with 60–62 Gy delivered for complete resection cases, and 66–70 Gy for cases with R1/R2 resection and definitive radiotherapy. Only one patient with a planned 67.84 Gy dose of radiation was stopped after 55.12 Gy for progressed disease; all

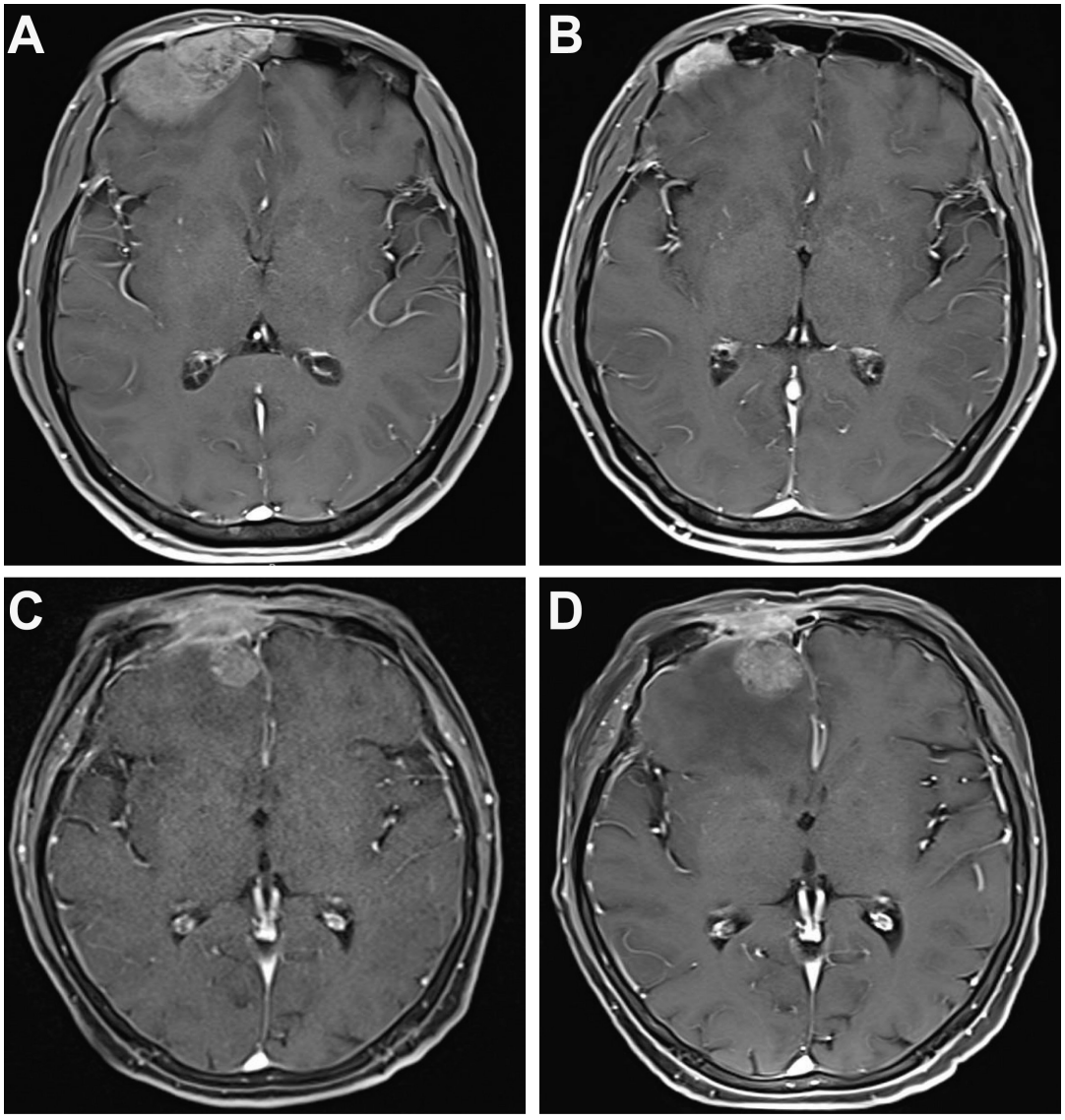

Figure 1. Contrast-enhanced T1-weighted MRI scan demonstrated a neoplasm with intense enhancement: A, B) partial response after induction chemotherapy; C, D) progressed disease after induction chemotherapy.

other patients showed a response to the concurrent chemoradiotherapy. Figure 3 presents the typical radiotherapy dose distribution in IMRT.

Follow-up. Follow-up data were available for 22 patients, and the follow-up period ranged from 4.4 to 78.4 months (median, 20.4). At the time of the most recent follow-up, 6 of 22 (27.3%) patients had died of this disease. Seven patients (31.8%) developed local recurrence. The mean time to local recurrence was 15.2 months (ranging from 6.2 to 25.9). Two patients had a regional failure, and one patient was found with distant metastases to the retroperitoneal lymph node.

Survivals. Kaplan-Meier survival curves for OS and DFS are shown in Figure 4. The median OS and PFS were 20.4 months and 17.2 months, respectively. The 1-, 2-, and 3-year OS for the whole cohort were 89.8%, 84.2%, and 45.1%, and. 1-, 2-, and 3-year PFS were 81.8%, 63.8%, and 31.9%, respectively. Patients who accepted chemoradiotherapy first had a better 2-year OS (100% vs. 72.7%, p=0.048) than those who accepted surgery first. However, there is no difference in 2-year PFS (53.0% vs. 75.8%, p=0.59) between the two groups. Patients with PD/SD after IC had more probability of developing local recurrence than other cases (Odds ratio = 19.7, p=0.007); they also showed poor 2-year PFS (40.0% vs. 82.1%, p=0.019).

There was no significant difference in 2-year OS (88.9% vs. 80.8%, p=0.95), or PFS (53.3% vs. 76.9%, p=0.52) between patients with and without brain invasion (Figure 5).

Discussion

SMARCB1, located on chromosome 22q11.2, is a highly conserved core subunit of the mammalian ATP-dependent BRG1/BRM-associated factor chromatin remodeling complex, a key regulator of nucleosome positioning and gene expression [7]. SMARCB1/INI1, ubiquitously expressed in all normal tissue nuclei, is vital in various interwoven factors in several pathways [8]. Loss of INI-1 expression has emerged as an important diagnostic feature in several malignancies, including atypical teratoid/rhabdoid tumors [9], liver cancer [10], vulvar tumor [11], renal carcinoma [12], synovial sarcoma [13], and central nervous system tumor [14]. INI-1 deficient sinonasal tumors exhibited significantly higher methylation levels with respect to INI-1-positive samples and had a worse prognosis [15]. Chitguppi et al. reported that SDSC showed worse overall survival (OS) and DFS than SNUC. Additionally, SDSC showed higher recurrence (75% vs. 17%) and mortality (67 vs. 14%) rates [16]. In a recent literature study of 128 patients, the 1-, 2-, and 3-year OS was 84.3%, 62.9%, and 51.8%, respectively, which is consistent with our cohort's outcomes, which were 89.8%, 84.2%, and 45.1%, respectively [17].

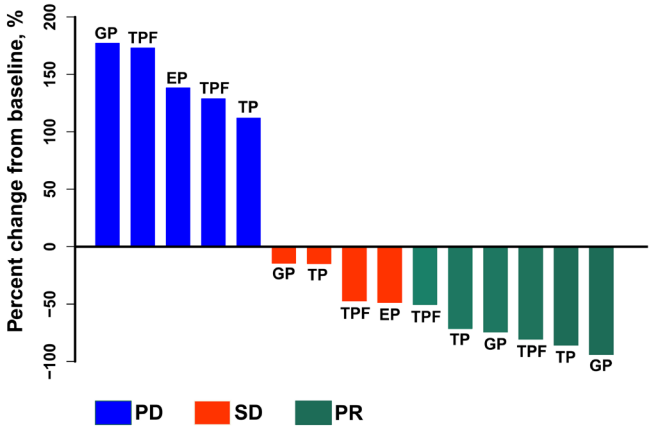

Figure 2. The waterfall plot presents the tumor response to the different induction chemotherapy modes. (TPF: docetaxel+cisplatin+fluorouracil; TP: docetaxel+cisplatin; GP: gemcitabine+cisplatin; EP: etoposide+cisplatin)

There is no consensus on the treatment mode for SDSC. Due to insufficient cases, the treatment modality is mainly based on case reports. Some investigators proved that target therapy on the enhancer of zeste homolog 2 (EZH2) inhibitors had demonstrated some antitumor activity in INI-1 deficient tumors [18]. The clinical benefits of immune checkpoint inhibitor therapy in SMARCB1-negative sarcoma have been reported in several pieces of literature [19]; However, there are no reports of application in SDSC.

Given the aggressive nature of this tumor, timely and effective treatment is critical. Sinonasal tumors are often treated with surgical excision followed by adjuvant radiation or concurrent chemoradiation. The most common cause of death was locally advanced unresectable disease [20]; with required surgery without complete tumor resection for locally advanced cases increasing operation difficulties and morbidity. It's worth investigating if chemotherapy or radiotherapy could be used before surgery.

Induction chemotherapy has proved to be helpful in SNUC in several investigations. London et al. [21] reported that patients managed by induction chemotherapy followed by concurrent chemoradiation showed no evidence of disease until the end of follow-up. Amit et al. [22] demonstrated that in patients who achieve a favorable response to IC, definitive CRT improved survival compared to those who undergo definitive surgery. Wang et al. [23] stated that for individuals with advanced SNUC, definitive-intent (chemo)radiotherapy could be the optimal treatment. According to Contrera et al. [24], patients who underwent induction chemotherapy were 76% less likely to die of diseases. In our study, 66.7% (10/15) of patients who accepted IC showed tumor decreasing, despite the fact that no chemotherapy method had a dominant priority. Patients with PD/SD in IC had poorer 2-year PFS (40.0% vs. 82.1%, p=0.019) than other cases and more probability of developing local recurrence (Odds ratios =19.7, p=0.007). However, less reaction to IC does not mean a poor response to radiation therapy. In our study, except for one patient, all other cases showed sensitivity to radiation therapy. Therefore, choosing the subsequent treatment step

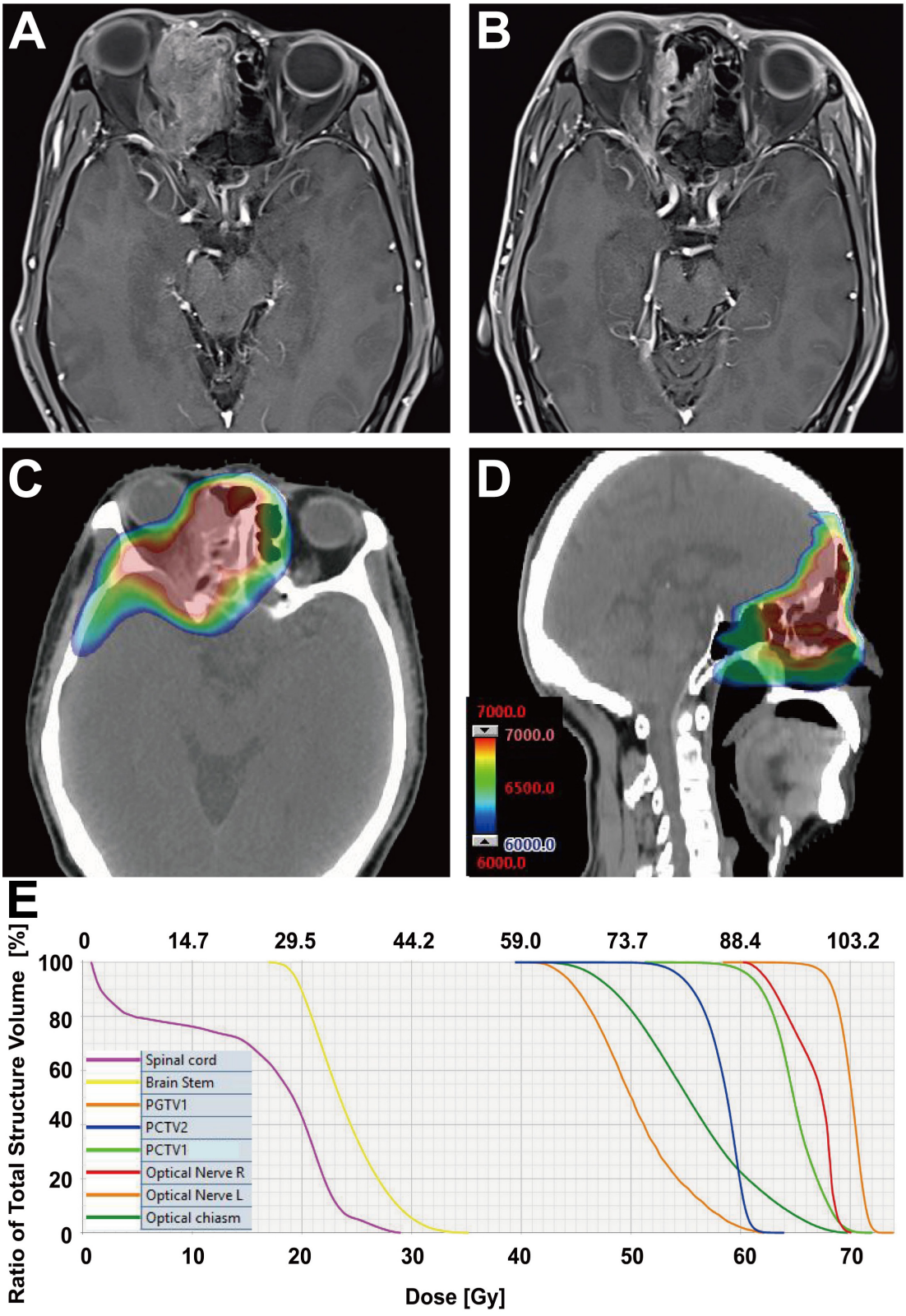

Figure 3. A patient with SDSC: A) shows an intense mass in the right nasal cavity and B) tumor regression after three cycles of induction. C, D) Dose distribution in IMRT. E) Dose-volume histogram

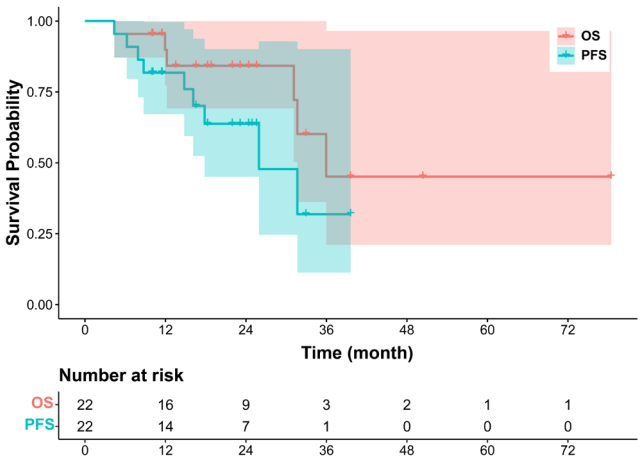

Figure 4. The Kaplan Meier analysis for 3-year overall survival (OS) rate and progression-free survival (PFS) rates in SMARCB1 (INI-1) deficient sinonasal tumor.

is another critical piece of the puzzle for patients who did not benefit from IC. Compared with patients who accepted surgery as a preference, patients who received chemoradiotherapy conferred a better 2-year OS (100% vs.72.7%, p=0.048). In this cohort, most patients (59.1%) had evidence of brain invasion, taking advantage of chemoradiotherapy in decreasing tumor burden; surgery acting as salvage for those with residual or progressed tumors might cause less trauma or complications after complete treatment.

In the current study of 22 patients with SDSC treated at our institution, the 3-year OS and PFS were less than 50%, indicating a poor prognosis. Most patients responded actively to the IC chemotherapy, and patients with PD/SD were more likely to develop local recurrence. Furthermore, patients who chose surgery had a worse overall survival than those who received chemoradiotherapy first. Therefore, for locally advanced SDSC, chemoradiotherapy might be managed before surgery, especially in patients who benefit from IC.

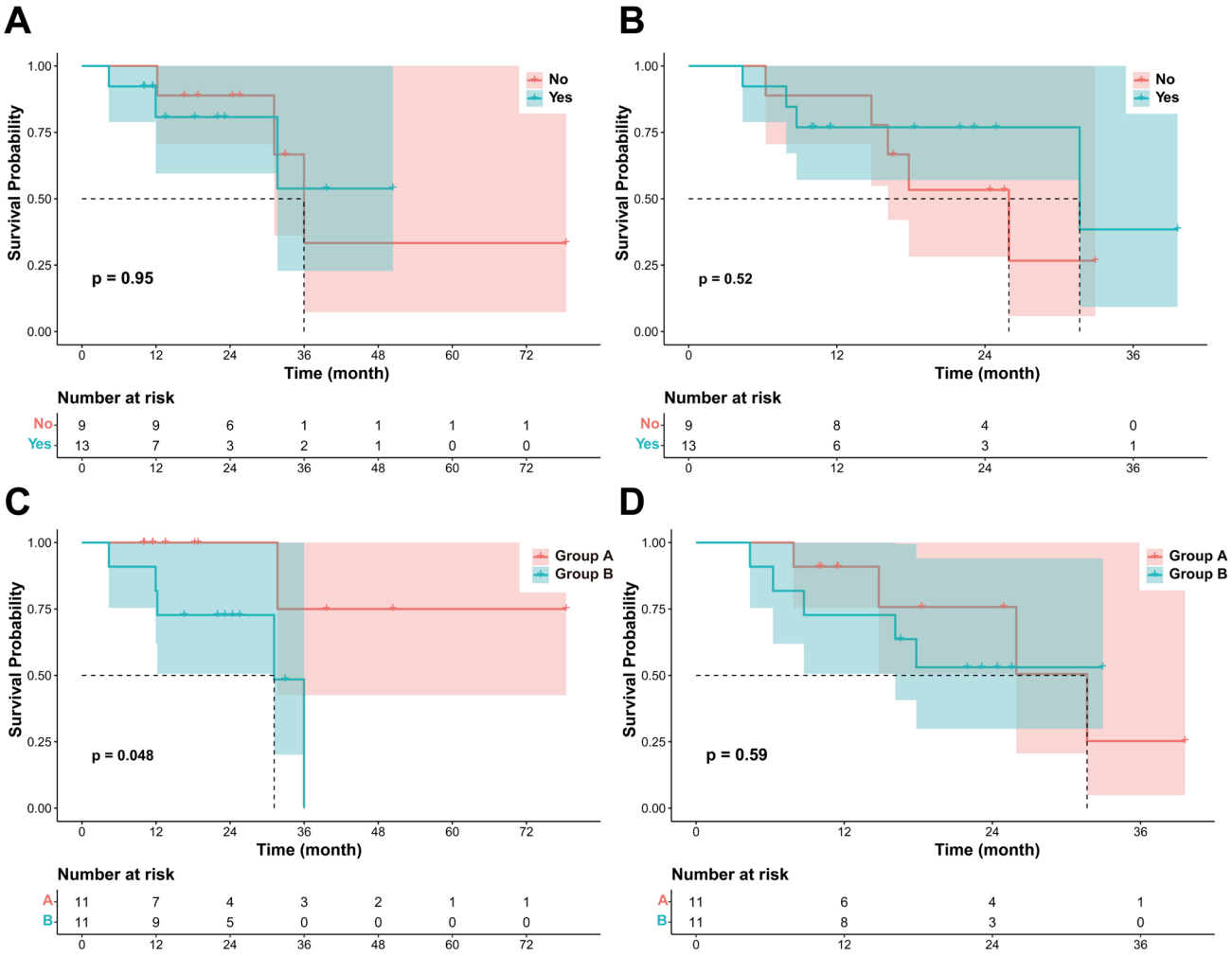

Figure 5. A, B) The Kaplan Meier analysis for 2-year OS (A) and PFS (B) in patients with or without brain invasion. C, D) Patients who accepted surgery first (Group B) showed a poor OS (p=0.048) but not PFS (p=0.59).

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