The role of histology on the outcome of sinonasal carcinomas treated with radiotherapy: a single institution experience

Ali Kazemian1,2,*, Borna Farazmand2,*, Maryam Taherioun3, Mahdie Razmkhah3, Mohammad Shirkhoda4, Amirmohsen Jalaeeifar5, Ata Garajati5,6, Mehrdad Jafari7, Farrokh Heidari8, Mahdi Aghili2,3, Reza Ghalehtaki2,3

1Department of Radiation Oncology, Cancer Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
2Radiation Oncology Research Center, Cancer Research Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
3Department of Radiation Oncology, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
4Department of Oncosurgery, Cancer Institute, Tehran University of Medical Sciences, Tehran, Iran
5Department of Head and Neck Surgical Oncology and Reconstructive Surgery, Cancer Institute, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
6Department of Oral and Maxillofacial Surgery, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran
7Department of Otologynology and Head and Neck Surgery, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
8Department of Otologynology and Head and Neck Surgery, Yas Hospital, Tehran University of Medical Sciences, Tehran, Iran

Received: September 15, 2022
Revised: November 20, 2023
Accepted: December 1, 2023

Correspondence:
Reza Ghalehtaki
Radiation Oncology Research Center, Cancer Research Institute, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Keshavarz Blvd, Tehran, Iran.
ORCID: https://orcid.org/0000-0003-1162-2019

*These authors contributed equally to this work.

Background: Sinonasal malignancies are a rare group of head and neck cancers. We aimed to report the oncological outcomes based on histological types in patients who underwent radiotherapy.

Materials and Methods: In this single-institution study, we retrospectively retrieved and analyzed data of patients with sinonasal carcinomas who underwent radiotherapy during 2011–2016 as part of their treatment. The 3-year rate of local, regional, and distant recurrences, and overall survival were evaluated according to the histological type.

Results: A total of 28 patients were evaluated in this study, the majority of whom were male (60%). Squamous cell carcinoma (SCC), adenoid cystic carcinoma (ACC), and adenocarcinoma (ADC) were found in 15 patients (53.5%), 8 (28.5%), and 5 (18%), respectively. The highest rates of local and regional recurrences were observed in ACC and SCC, respectively. Distant recurrences were numerically more common in ADC. The 3-year OS was 48%, 50%, and 73% in SCC, ADC, and ACC, respectively.

Conclusion: Different histopathologies of sinonasal cancer seem to have different patterns of failure, and this may be considered in the treatment approach.

Keywords: Adenoid cystic carcinoma, Treatment outcome, Squamous cell carcinoma, Head and neck neoplasms, Radiotherapy, Paranasal sinus neoplasms

Introduction

Sinonasal malignancies are a rare group of head and neck cancers with various histological types, accounting for nearly 3%–5% of all head and neck cancers. Squamous cell carcinoma (SCC) is the most common type [1], and nasal cavity and maxillary antrum are the most common involved sites [2,3]. The mean age at diagnosis is approximately 62–66 years and the incidence is higher in men than women [3,4]. These tumors have nonspecific symptoms in early stages, most patients present with advanced disease at the time of diagnosis [3,5].
Because of rarity and heterogenicity of these tumors, we cannot rely on randomized clinical trials to determine the best management approach, and single-institution retrospective studies provided most of the available data [6,7].

Surgery, either endoscopic or open, with the goal of achieving complete resection with negative margins, is considered the mainstay of treatment [8]. The National Comprehensive Cancer Network guidelines recommend upfront surgery in resectable sinonasal tumors, and reserve definitive radiotherapy with or without chemotherapy for unresectable/inoperable cases [9].

However, complete resection with favorable functional outcome can be challenging in these anatomic sites, due to its proximity to vital structures, such as the orbit, brain, cranial nerves, and carotid arteries [10]. So, postoperative radiotherapy with or without concurrent systemic therapy, is often needed [11]. In fact, the use of surgery alone is only acceptable for early T1 or T2 low-grade lesions that can be resected to negative margins, especially those localized to the lower sinonasal cavity. Generally, the treatment of patients with a locally advanced lesion involves definitive concurrent chemoradiotherapy, or surgery followed by postoperative radiotherapy with or without chemotherapy for selected cases [12].

Five-year overall survival (OS) is in the range of 27%–67% overall [1,13], but there is a variation between different histological types.

Since sinonasal cancers constitute a relatively small proportion of head and neck malignancies, further information, especially on various histological types, can improve the clinicians’ decision-making process. In case of different oncological outcomes of various histological types, approaching these tumors based on histology is reasonable. Therefore, the present study aimed to describe the effects of histological types, including SCC, adenocarcinoma (ADC), and adenoid cystic carcinoma (ACC), on the outcomes of patients with sinonasal tumors, who were treated with radiotherapy in our cancer center.

Materials and Methods

1. Study design
In this retrospective cohort study, patients with sinonasal cancer who were treated with radiotherapy during 2011–2016 at the Cancer Institute of Iran, affiliated to Tehran University of Medical Sciences, were evaluated. The records of patients whose disease was confirmed by pathology were retrieved from the patients’ medical records. This study was approved by the Institutional Ethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.IKHC.REC.1399.102).

2. Patients’ characteristics
All patients with a history of sinonasal cancer in any sinuses of the maxillary, ethmoid, sphenoid, frontal, and nasal cavities, who received radiotherapy as part of their treatment, were included in this study. The exclusion criteria were lymphoma, melanoma, or sarcoma histology and distant metastasis at the time of treatment.

3. Pretreatment analysis
The pretreatment workup consisted of history-taking, physical examination, fiber optic nasal endoscopy, transoral or transnasal biopsy, and magnetic resonance imaging (MRI) or computed tomography (CT) scan of the primary tumor location and the neck for local and regional staging. The 7th version of American Joint Committee on Cancer (AJCC) staging system was used for staging. The areas of involvement were defined in the workups. Pulmonary metastasis was examined by chest X-ray or CT scan at the physician’s discretion based on locoregional staging.

4. Surgery
Although surgery is the mainstay of treatment for sinonasal carcinomas, it is challenging to obtain sufficient margins considering the complex anatomy of paranasal sinuses. Besides, it is important to determine when a tumor is deemed unresectable. Relative dependence on the surgeon’s experience, ability to reach free margins, morbidities of the procedure, and reconstruction options may affect operability. In our institute, based on the available evidence, anatomic contraindications for open, endoscopic, or combined surgeries include gross brain invasion, central skull base or extensive dural invasion, bilateral optic nerve, orbital apex, or chiasm infiltration, and cavernous sinus invasion. Inoperable cases commonly include extension through the sphenoid sinus walls which usually suggests invasion to the carotid arteries or the cavernous sinus, cutaneous nodularity due to tumor spread, significant trismus with gross involvement of the pterygoid and masticatory musculature (for which it is not possible to obtain a sufficient margin), and carotid encasement or prevertebral involvement because of lymph node involvement [14].

1) Histological examination
During histological examinations by pathologists, three main histological types, including SCC, ACC, and ADC, were differentiated. Commonly, these carcinomas are easily diagnosed via hematoxylin and eosin staining under light microscopy. For challenging cases that may seldom occur, ancillary studies, such as immunohistochemistry, are needed to better define the histological type.
2) Radiotherapy
The indications for postoperative radiotherapy included a positive, close, or indeterminate surgical margin, perineural (PNI) or lympho-vascular invasion (LVI), T3/T4 tumor, extranodal extension (ENE), and multiple lymph node involvement. In locoregionally advanced tumors (T3/T4 or node-positive), surgery and adjuvant radiotherapy were applied for operable cases and concurrent chemoradiotherapy with or without induction chemotherapy for unresectable or inoperable cases.

Our department protocol for three-dimensional (3D) conformal radiotherapy was applied for simulation and treatment planning. Data obtained from the physical examinations, MRI or CT scans, and/or surgical pathology reports were used for target volume delineation. The patients were immobilized by a thermoplastic mask. Their head was extended for CT simulation and during treatment sessions. The gross tumor volume (GTV) was defined as all gross disease on physical examination and imaging or any postoperative residual disease. The clinical target volume (CTV) was defined as GTV plus an anatomical margin of 1–1.5 cm. Finally, the planning target volume was defined as CTV plus a geometrical margin of 0.5 cm.

In the adjuvant group, the prescribed dose to the high-risk regions was 60 Gy for negative margins and 66 Gy for positive margins or ENE. This volume included resection bed, areas of ENE, and all areas of initial disease. Low-risk regions, including non-violated neck and cranial nerves (if indicated) received 46–50 Gy radiotherapy. In definitive cases, the prescribed dose to the high-risk region was 70 Gy, which included gross tumors or nodes with short axis diameter greater than 1 cm. A dose of 60 Gy for was prescribed to the intermediate-risk regions, including areas of suspected microscopic extension surrounding primary tumor or smaller than 1 cm involved nodes. And finally, 46–50 Gy radiotherapy was delivered to the low-risk regions including elective lymph nodes and cranial nerves (if indicated). Indications for coverage of cranial nerves in both settings were ACC histology and/or PNI. The main photon energy level was 6 MV (Fig. 1).

3) Chemotherapy
Induction chemotherapy was given to patients with unresectable bulky tumors or nodes to shrink the 70 Gy volume of radiotherapy so the patients would better tolerate the entire radiotherapy course. Also, another theoretical advantage of induction chemotherapy in patients with N2-3 disease is to lower the chance of distant dissemination of tumor during the local therapy. Induction chemotherapy regimens for advanced disease were docetaxel/cisplatin/fluorouracil (TPF; 75 mg/m$^2$ of docetaxel on day 1, 75 mg/m$^2$ of cisplatin on day 1, and 750 mg/m$^2$ of fluorouracil on days 1–5 via continuous intravenous infusion) or cisplatin/ fluorouracil (PF; 60 mg/m$^2$ of cisplatin on day 1 and intravenous infusion of 800 mg/m$^2$ of fluorouracil on days 1–5) every 3 weeks for 1–3 cycles.

Cisplatin (30-35 mg/m$^2$ weekly or 100 mg/m$^2$ every 3 weeks) was the concurrent adjuvant chemoradiotherapy regimen for patients with major or several minor postoperative risk factors. The major risk factors included ENE and positive surgical margins, while the minor risk factors included T3 or T4 primary tumor, PNI or LVI,

Fig. 1. Picture shows dose distribution of a patients with maxillary sinus squamous cell carcinoma undergoing three-dimensional conformal radiotherapy (blue 36 Gy, green 54 Gy, and pink 57 Gy). (A) shows a proximal cut of the axial section, (B) shows a distal cut of the treated volume, (C) shows the sagittal view of the treated area.
bone invasion, and involvement of lower neck nodes. In patients who were not eligible for cisplatin, cetuximab (400 mg/m² 1 week before radiotherapy, then 250 mg/m² weekly) were given. Concurrent chemotherapy with adjuvant radiotherapy was not indicated for patients older than 60 years of age and those with underlying comorbidities that would risk the patient’s compliance to planned radiotherapy in case of receiving chemotherapy.

In definitive cases, all patients with T3/T4 primary tumors or node-positive neck received concurrent chemoradiotherapy with the same regimen. Concurrent chemotherapy with definitive radiotherapy was not indicated for patients older than 70 years of age.

5. Patient assessment during treatment

The patients were assessed by radiation oncologists using physical examination and laboratory tests. They were evaluated at least weekly during radiotherapy and every 3 weeks during induction chemotherapy.

6. Post-treatment follow-up

In the postoperative setting, 3 months after radiotherapy, patients were assessed by CT scan or MRI at baseline. The physical examination was repeated every 3–4 months for the first 2 years, every 6 months in the third year, and then annually; imaging was performed as a main part of the follow-up care routine.

For the definitive radiotherapy group, the primary assessment was performed at 8–12 weeks post-treatment to assess the patients’ clinical response. Also, the interval between the follow-up visits was shorter in the first 2 years, i.e., every 2–3 months maximum, after which it matched that of the adjuvant group.

7. Study outcomes and statistical analysis

All eligible patients were recruited consecutively in this study, without sample size or power calculation. SPSS version 20.0 (IBM Corporation, Chicago, IL, USA) was used to analyze the data. To compare the characteristics of various histological types, chi-square test was performed. Also, to calculate the OS and disease-free survival (DFS) rates, Kaplan-Meier survival analysis was performed. The median follow-up duration was calculated for the survivors, using the reverse Kaplan-Meier survival curve method. The OS was calculated from the termination of radiotherapy until the last follow-up or death. The end-point for DFS was the occurrence of locoregional or distant metastasis or death. The local recurrence (LR) was defined as the recurrence of the tumor in the surgical bed or the previous GTV volume. The distant metastasis (DM) was defined as the recurrence of tumor in other organs such as lung, liver and bone or also non-regional lymph nodes. The regional recurrence (RR) was defined as recurrence in neck lymph nodes. All of the LR or RRs should be confirmed by the biopsy. The occurrence of LR or DM was considered when calculating recurrence rate overall recurrence of the tumor. Also, to determine significant differences between the histological types in terms of OS and DFS, the log-rank test was used. The level of statistical significance was set at \( p < 0.05 \).

Results

1. Patients’ characteristics

In this study, a total of 28 patients were included in the analysis; patients’ characteristics are detailed in Table 1. Overall, 60% of the patients were male. SCC and ADC were more common in men, with prevalence rates of 73% (11 out of 15) and 80% (4 out of 5), respectively, whereas ACC was three times more prevalent in women. Regarding the histological type, SCC, ACC, and ADC were detected in 15 patients (53.5%), eight (28.5%), and five (18%), respectively (Table 1).

Most of the patients in this study had locoregionally advanced disease (71.4% stage III or IV; 20 out of 28). Half of the patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Maxillary sinus</th>
<th>Ethmoid sinus</th>
<th>Nasal cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>26 (92.8)</td>
<td>1 (3.6)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Stage I</td>
<td>1 (3.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage II</td>
<td>7 (25.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage III</td>
<td>6 (21.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>14 (50.0)</td>
<td>8 (53.3)</td>
<td>3 (60.0)</td>
</tr>
</tbody>
</table>

Values are presented as median (range) or number (%). SCC, squamous cell carcinoma; ADC, adenocarcinoma; ACC, adenoid cystic carcinoma.

![Table 1. Baseline characteristic in all patients and each histology](https://doi.org/10.3857/roj.2022.00514)
were stage IV (14 out of 28). The most common tumor site was the maxillary sinus, as detected in 26 (92.8%) cases. Other sites of primary tumors were the ethmoid sinus in one patient (3.6%) and the nasal cavity in one patient (3.6%).

2. Treatment characteristics
Treatment characteristic according to histology is shown in Table 2. In this study, 20 patients (71.4%) underwent surgery and out of those, according to the surgical pathology report, 13 patients had a positive margin (R1 resection), while seven patients had negative margins. No patient had gross residual disease after surgery (R2 resection). Four of the resected tumors exhibited LVI. The LVI was seen in 1 tumor (7.1%), 2 (40%), and 1 (50%) in resected SCC, ACC, and ADC, respectively (p = 0.165). Also, eight patients showed PNI, as reported in 2 cases (15.4%), 5 (100%), and 1 (50%) of resected SCC, ACC, and ADC (p = 0.004), respectively.

Half of the patients underwent radiotherapy to the primary site as the target volume, while others also received radiotherapy to the lymph nodes of the neck. Only three SCC patients underwent induction chemotherapy, consisting of a TPF regimen before radiotherapy. Concurrent chemotherapy was prescribed for 11 patients, eight of whom received cisplatin weekly (SCC 6, ADC 1, and ACC 1), two received cisplatin every 3 weeks (ADC), and one received cetuximab (SCC).

3. Disease outcomes
In this study the pattern of recurrence during the 40 month median follow-up (range. 1 to 73 months) is shown in Table 3. The major type of recurrence was DM in nine patients (32%). Local, regional, and distant recurrences occurred in 4 patients (14.3%), 3 (10.7%), and 9 (32.1%), respectively. Overall, four patients (44% of all recurrences) showed both DM and LR. Considering histopathology, three patients (20%) with SCC showed regional recurrence, while none of the ACC or ADC showed RR. Of patients with RR, two patients (66.7%) had been received neck radiotherapy (one was N0 and another was N2) and one patient (33.3%) received primary tumor radiotherapy alone (N0). The rate of LR in patients with ADC, SCC and ACC was 0 (0%), 2 (13.3%) and 2 (25%), respectively. Of the patients who experienced LR, all underwent surgery and two patients (50%) had involved surgical margin. Also, the histology with numerically highest rate of distant metastasis was ADC (2 patients, 40%). The frequency of distant metastasis in SCC and ACC was 4 (26.7%) and 3 (37.5%), respectively. LR was reported in 2 (50%) of metastatic patients with SCC (2 out of 4) and ADC (1 out of 2) versus 66.7% of patients with ACC (2 out of 3).

In this study, 10 patients expired during the follow-up. The median OS for SCC, ADC, and ACC was 24, 35, months, and not reached, respectively (p for log-rank test = 0.376) (Fig. 2). The median DFS for SCC, ADC, and ACC was 21, 33, and 23 months, respectively (p for log-rank test = 0.434) (Fig. 3). Table 4 shows the 3-year outcomes based on the histology.

### Table 2. Treatment characteristics in all patients and each histology

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 28)</th>
<th>SCC (n = 15)</th>
<th>ADC (n = 5)</th>
<th>ACC (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical resection</td>
<td>Yes</td>
<td>20 (71.4)</td>
<td>13 (86.7)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>8 (28.6)</td>
<td>2 (13.3)</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>Radicals of resection</td>
<td>R0</td>
<td>7 (35.0)</td>
<td>5 (38.5)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td></td>
<td>R1</td>
<td>13 (65.0)</td>
<td>8 (61.5)</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>Regional radiotherapy</td>
<td>In N0</td>
<td>6 (30.0)</td>
<td>3 (33.3)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td></td>
<td>In N+</td>
<td>8 (100)</td>
<td>6 (100)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>14 (50.0)</td>
<td>9 (60.0)</td>
<td>3 (60.0)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Total radiotherapy dose</td>
<td>60 (50–70)</td>
<td>60 (50–70)</td>
<td>66 (60–70)</td>
<td>66 (50–70)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>Induction</td>
<td>3 (10.7)</td>
<td>2 (13.3)</td>
<td>1 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Concurrent</td>
<td>11 (39.3)</td>
<td>8 (53.3)</td>
<td>2 (40.0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (range).

SCC, squamous cell carcinoma; ADC, adenocarcinoma; ACC, adeno cystic carcinoma.

### Table 3. Pattern of recurrence based on histology

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 28)</th>
<th>SCC (n = 15)</th>
<th>ADC (n = 5)</th>
<th>ACC (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any type of recurrence</td>
<td>9 (32.1)</td>
<td>4 (26.6)</td>
<td>2 (40.0)</td>
<td>3 (37.5)</td>
</tr>
<tr>
<td>Local recurrence alone</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Local recurrence overall</td>
<td>4 (14.3)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
<td>2 (40.0)</td>
</tr>
<tr>
<td>Regional (neck) recurrence alone</td>
<td>1 (6.7)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Regional (neck) recurrence overall</td>
<td>3 (10.7)</td>
<td>3 (20.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Distant recurrence alone</td>
<td>4 (14.3)</td>
<td>0 (0)</td>
<td>2 (40.0)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Distant recurrence overall</td>
<td>9 (32.1)</td>
<td>4 (26.6)</td>
<td>2 (40.0)</td>
<td>3 (37.5)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

SCC, squamous cell carcinoma; ADC, adenocarcinoma; ACC, adeno cystic carcinoma.

### Discussion and Conclusion

Sinonasal cancers are rare cancers of head and neck, so very few prospective trials are conducted and most recommendations are based on single-institution retrospective analyses. Due to heterogeneity, it is important to report detailed information about pa-
In this study, the primary site of most tumors was maxillary sinus (26 out of 28 patients). Although nasal cavity is the most common primary site in many studies [4], maxillary sinus tumors are more prevalent in some studies that reported only sinonasal cancer patients who were treated with radiotherapy [7].

Outcomes are poor with 5-year OS in the range of 27%–67% [5], but differs significantly between histologic subtypes, with the worst prognosis reported for SCC, ACC, and ADC [6]. In the present study, the three-year survival rate was 56%, which is comparable to other older studies [15] but inferior to others using modern techniques like intensity-modulated radiotherapy (IMRT) [16].

SCC, was the most common histopathology in this study, affecting more than half of our patients (15 patients, 53.6%). SCC had the highest rate of node-positive disease (6 patients, 40%) as an indication for radiotherapy and highest rate of RR (3 patients, 20%). Although it had the highest rate of surgical resection at presentation (13 patients, 86.7%), eight patients had R1 resection (61.5%). After radiotherapy, only two patients recurred locally (13.3%). In the follow-up of patients with this pathology, the 3-year OS rate and the median OS were 48% and 28 months, respectively, which are comparable to the results of previous studies [6].

ACC was reported in eight patients, with 3:1 ratio for female (6 vs. 2 patients). Expectedly, lymph node involvement was low in ACC. Overall, 87.5% of the patients presented with node-negative necks, and the remaining had N1 disease. None of the patients showed regional recurrence. Bone invasion was detected in 87% of the patients, which is similar to SCC. According to AJCC staging, half of the patients presented with T3 or T4 tumors and the highest LR rate was observed in patients with ACC (25%). In our study, 37% of the patients showed distant metastasis. The 3-year OS rate and median OS were 48% and 28 months, respectively; these rates are comparable to the reports of other studies indicating histology-specific survival rates [15]. This pathology had the highest survival rate, despite a relatively high local failure and distant metastasis rate, indicating an indolent course of disease progression, especially in distant sites. Previous studies reported that most of the patients died.

Table 4. Three-year rates of local recurrence and distant metastasis, recurrence rate, disease-free survival, and overall survival

<table>
<thead>
<tr>
<th>Histology</th>
<th>Local recurrence</th>
<th>Distant metastasis</th>
<th>Any recurrence</th>
<th>Disease-free survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>25</td>
<td>44</td>
<td>67</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>ACC</td>
<td>32</td>
<td>43</td>
<td>43</td>
<td>50</td>
<td>73</td>
</tr>
<tr>
<td>ADC</td>
<td>0</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

SCC, squamous cell carcinoma; ADC, adenocarcinoma; ACC, adenoid cystic carcinoma.
from LR rather than DM, and PNI affects the survival rate [17].

ADC were diagnosed in five patients. All the patients had a locally advanced disease (T3-T4), and 80% of them had NO disease. In our cohort, ADC had the highest definitive radiotherapy rate. In ADC, due to the fact that all the studied patients had received radiotherapy, LR or RR was not detected, although the highest rate of DM was reported. This is in contrast with other studies, where LR is the main cause of treatment failure (about 30%) [18], and lymph node metastasis and DM occur in nearly 10% and 13% of the patients, respectively [19]. The sphenoid sinus involvement, T4 stage, and higher-grade histology significantly decreased the rate of survival [20]. The 3-year OS rate was 50%, and the median OS was 42 months; this rate is similar to that of SCC, but lower than that of ACC, indicating a more aggressive DM course in ADC.

Our most important limitation is that we only reported the outcomes of patients who all underwent radiotherapy so this limitation would negatively influence the external validity of our study when investigating patients with sinonasal malignancy. Second limitation of this study was the use of 3D-conformal technique for all of the patients, instead newer, more advanced, techniques. A study by Bahig et al. [6] from MD Anderson Cancer Center, reported the outcomes of patients treated with advanced-technique radiotherapy, including IMRT or proton therapy. They reported an impressive 5-year OS of 65%. However, the lowest 5-year OS in this study was attributable to ADC, SCC, and ACC with the rate of 22%, 38%, and 42%, respectively. The highest 5-year OS was seen inesthesioneuroblastoma and neuroendocrine carcinoma (75% and 72%, respectively). So, the difference of OS from our study, can partially be explained by this difference in histology distribution. Also, some believe that the most important advantage of IMRT is in its improved toxicity profile, with comparative effectiveness compared to conventional techniques [5]. Unfortunately, we did not have toxicity rate in the patients treated in this study.

Another main limitation of this study was the small number of patients and heterogeneity of patients, disease characteristics, and treatment methods, which limits statistical analysis; however, this is the case in most studies about sinonasal malignancies. Another limitation would be inability to use 18fluoro-deoxy-glucose positron emission tomography/computed tomography scan for equivocal MRI and CT findings to help have a proper staging and delineate target volumes during radiotherapy. These major limitations would also affect our comparison of treatment outcomes between our study and others.

In conclusion, the type of histology seems to have an effect on the oncological outcomes of patients with sinonasal cancers who underwent radiotherapy. This relationship may guide the treatment approaches used for the management of malignant sinonasal tumors and also the need for systemic or local work-up during post-treatment follow-up. Based on results of this study, similar articles, and extrapolation from other head and neck cancer sites, patients with SCC may require a more vigorous local treatment to prevent locoregional recurrence, along with a relatively weak systemic therapy to lower the modest chance of distant failure. Systemic therapy, in addition to radiotherapy, may be emphasized for patients with ADC to avoid DM as the primary cause of treatment failure. Considering the very low rates of local and regional failure, radiotherapy alone can be a sufficient local treatment for ADC. Patients with ACC expect a long disease course, therefore, care services may include quality of life considerations and a robust local treatment whenever possible, even for metastatic cases.

**Statement of Ethics**

This study was approved by the Institutional Ethics Committee of Tehran University of Medical Sciences (No. IR.TUMS.IKHC.REC.1399.102). Written informed consents were obtained.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Acknowledgements**

We thank our colleagues from Department of Radiation Oncology of Cancer Institute, Imam Khomeini Hospital Complex for their contribution in patients’ accrual and enrollment. We are deeply grateful of our beloved clerks in Medical Records Archive who helped us a lot during data collection.

**Funding**

This study was supported and funded by the Tehran University of Medical Sciences (Grant No. 99-1-248-47949).

**Author Contributions**

Conceptualization, AK, BF, RG, MR; Investigation and methodology, AK, BF, RG, MR; Writing of the original draft, AK, BF, RG, MT, MR, MS, AJ, AG, MJ, FH, MA; Writing of the review and editing, AK, BF, RG, MT, MR, MS, AJ, AG, MJ, FH, MA; Software, AK, BF, RG, MT, MR; Formal analysis, AK, BF, RG, MR; Data curation, AK, BF, RG, MT, MR, MS, AJ, AG, MJ, FH, MA.
Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References