CHAPTER VI

CLINICAL AND TREATMENT CHARACTERISTICS OF PARANASAL SINUS AND NASAL CAVITY CANCERS

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1. Introduction

Paranasal sinus and nasal cavity cancers are very rare and constitute approximately 3% of all head and neck malignancies (1-3). They constitute a highly heterogeneous group of malignancies in terms of both localization and histological type (1,3). Although distant metastasis and lymph node involvement are not common, topographic anatomical features have some difficulties in local treatment because of the functional and vital features of the surrounding structures and local recurrence rates are quite high (1-4).

Multidisciplinary oncological approach with pre-treatment evaluation and staging is very important in treatment plans of patients with paranasal sinus and nasal cavity cancer (1,4). As with other head and neck cancers, the most effective and important treatment approach that contributes to survival in patients with both paranasal sinus and nasal cavity cancer is the initial treatment option. Because even if salvage surgery or salvage radiation treatments are successful in suitable patients, the first treatment plan has been reported to be more effective especially in local disease (5-8). Often, progressive outcome of initial treatment failure occurs within the first 2 years of diagnosis. Therefore, it is very important that the patients are closely followed up especially during the first 2 years (5, 7-9). In addition; almost 33% of these patients develop a second primary cancer in the respiratory and gastrointestinal tracts. Because of this risk, it is important to follow up and evaluate patients with paranasal sinus cancer for second primary cancers (1,2,4,8).
This article includes the current literature on the clinical and therapeutic features of paranasal sinus and nasal cavity cancers that do not have adequate treatment and prognosis data due to their rarity.

2. Epidemiological and histopathological features

Nasal cavity and paranasal sinus cancers, which are frequently considered together, are often diagnosed as advanced stage disease and have a poor prognosis (5,7,8). According to the literature information, it is more common in men than in women (1,2,4).

Squamous cell carcinoma accounts for approximately 70-80% of all paranasal sinus and nasal cavity cancers. Adenocarcinoma is the majority of the remaining histological subtypes (1,4). In squamous cell carcinoma, the tumor mass often grows into the bone structures of the sinuses and often remains asymptomatic unless erosion or invasion into adjacent structures (1,4,6).

Minor salivary gland tumors (adenoid cystic carcinoma, adenocarcinoma and mucoepidermoid carcinoma) account for approximately 10-15% of paranasal sinus and nasal cavity cancers, except squamous cell carcinoma (9-12). Malignant lymphomas constitute approximately 5% of all cases, while malignant melanoma, poorly differentiated carcinoma, angiosarcoma, rhabdomyosarcoma and olfactory neuroblastoma (esthesioneuroblastoma) are seen in less than 1% of patients (9-13).

Paranasal sinus cancers most commonly develop from the maxillary sinuses (6,11). While cancers of the ethmoid sinus, nasal vestibule and nasal cavity are less common, cancers of the sphenoid and frontal sinuses are very rare (6,8,11).

The features of paranasal sinus cancers are not frequent nodal involvement in the early stages (6,9,11). For sinus malignancies, the first step of lymphatic drainage is the retropharyngeal lymph nodes. In addition, depending on the location of the primary tumor, periparotid, cervical 1B and 2 level lymph nodes are also frequently involved. The main lymphatic drainage of the maxillary sinus is the first station via submandibular, parotid and jugulodigastric lymph nodes, lateral and inferior trunks, and retropharyngeal and jugular nodes superoposterior trunks (9). The frequency of lymph node involvement in paranasal sinus cancers varies depending on the local spread of the primary tumor to the surrounding structures (9,11). Lymph node metastasis is more common in T2 tumors than squamous cell carcinoma of maxillary sinus than T3 or T4 tumors (9,12).
Distant metastasis occurs rarely at the time of diagnosis and after primary treatment, but lung, liver and bone are the most common sites of metastasis (1,9,11). Even though distant metastasis develops in 20-40% of both nasal cavity and paranasal sinus cancer patients, these patients often die due to the direct spread to important structures in the skull due to rapid progression of regional and local disease (9,11).

3. Etiology and risk factors

It has been reported that the most important etiological factor in cancers of paranasal sinuses and nasal cavity is exposure to some industrial substances such as leather industry, textiles, wood dusts, formaldehyde, and tobacco exposure (6,14). It is thought that the incidence of second primary head and neck tumors is increased in patients at this risk (7,11).

It has been reported that some of the patients with paranasal sinus and nasal cavity squamous cell carcinoma are associated with human papilloma virus [HPV] and HPV positive patients have a better prognosis than HPV negative ones (14,15). There are studies showing the association of HPV with malignant degeneration of inverted papilloma, which is a rare and generally accepted benign condition (15). Similarly, there is a relationship between Epstein-Barr virus infection and sinonasal lymphomas (16).

4. Clinical features

Paranasal sinus malignancies are usually asymptomatic until they invade into neighboring structures or present with nonspecific symptoms resembling benign diseases of the sinonasal region (1,6,17). The most common symptoms include facial or toothache, nasal obstruction, and epistaxis (6,17). Paranasal sinus, nasal vestibule and nasopharyngeal cancers should be considered in differential diagnosis in patients over 40 years of age with persistent nasal discharge and epistaxis (6,17,18). Rare symptoms include chronic sinusitis, facial edema, loss of vision, headache, rhinorrhea, and hyposmia, as well as cranial neuropathy such as abnormalities in trigeminal neuralgia and extraocular movements (17,18). Moreover, 40-60% of patients with advanced paranasal sinus cancer have a classic triad of facial asymmetry, palpable or visible tumor in the oral cavity and visible intranasal tumor (17,18).

Symptoms and signs depend on the location of the primary tumor and the extent of the disease. Cancer invasion is very easy because the bone structures between the nasal cavity, sinuses, orbital and cranial cavities are mostly thin (17,19). Locally advanced lesions of the ethmoid sinus may spread through the cribriforme plate into the anterior cranial fossa or the orbit along the lamina papyracea, resulting in the patient's
anosmia or ocular displacement typically upward and / or downward (17,19). Sphenoid sinus tumors can spread directly to the cavernous sinus through cranial nerves III, IV, VI, V1 and V2 along the lateral bone wall and may also invade the middle cranial fossa directly or via the infraorbital nerve. In these patients, diplopia, blurred vision, proptosis, paresthesia may develop due to damage to the trigeminal nerve and trismus may develop in case of pterygoid muscle invasion. In addition, if it spreads into the oral cavity, it may cause painful tooth loss (6,17,18).

5. Staging

It is important to predict the prevalence of the disease in clinical staging (16). Therefore, in all cases, it is recommended to evaluate both primary tumor and possible lead node involvement by inspection, palpation and direct endoscopic examination (16,17). Biopsy for histological typing should be performed following the initial evaluation (17).

Computed tomography and / or magnetic resonance imaging studies are necessary to determine the prevalence of the disease prior to surgical treatment or curative radiotherapy and to distinguish other causes such as infection, secretion plug or granulation tissue (6,17,18). The same evaluation before the treatment plan for relapse is very important, especially in patients undergoing salvage surgery or salvage re-irradiation (17). Unlike other head and neck tumors, staging for paranasal sinus and nasal cavity cancers has not been clearly established. Although not used for staging of lymphoma, mucosal melanomas and sarcomas, Tumor (T), Nod (N), Metastasis (M) [TNM] staging system which is published by American Joint Committee on Cancer (AJCC) in 2017 is preferred for maxillary sinus, ethmoid sinus and nasal cavity cancers. Information on staging is shown in Table 1 and Table 2 (18).

6. Treatment options (Table 3)

When the literature data are reviewed, there is no clear consensus and a randomized study for the optimal treatment of paranasal sinus and nasal cavity cancers, since they are rare tumors and heterogeneous in both histological type and location of the primary tumor (19).

Regardless of nodal involvement, the standard treatment for maxillary and ethmoid sinus adenocarcinomas or squamous cell carcinomas in all T1-T4 tumors is surgical resection, if possible. However, because of the risk of complications such as damage to critical structures such as eyes, brain and cranial nerves, surgical resection is often limited due to primary tumor involvement (7,19-23). Therefore, considering the technological advances for reconstructive approaches and improvements in increasing the quality of life, the decision whether to
undergo surgical treatment in paranasal sinus cancers should be made in a way to include survival, morbidity and functional evaluation (7,19-23).

Local invasion is often common even in early stage lesions in squamous cell carcinoma and adenocarcinomas of the paranasal sinuses and the risk of local recurrence after complete resection is very high in patients who do not receive adjuvant radiation therapy after surgical resection (20,21). Therefore, postoperative radiotherapy should be recommended in the presence of conditions such as poor or positive surgical margin, poorly differentiated histology and perineural invasion, which are considered as poor prognostic factors especially for local recurrence in Stage I and II patients (19,20).

Due to the tendency of early invasion to nearby tissues, it is recommended to evaluate the local spread characteristics of the patients well before resection to determine the most appropriate surgical approach (20-26). The demonstration of orbital involvement is particularly valuable for surgical technique, local recurrence risk and morbidity. Before surgical resection, it is important to evaluate the patients with computed tomography and magnetic resonance imaging and to determine the stage of orbital invasion (26,27). The orbital invasion stage is defined in 3 degrees as follows (27):

- Grade I invasion; destruction of the medial orbital wall
- Grade II invasion; invasion of extraconal periorbital adipose tissue
- Grade III invasion; medial rectus, optic nerve, bulbus, eyelid skin invasion

Orbital exenteration is recommended only for patients with grade III orbital invasion (27). For this approach, however, it is often necessary to determine whether the tumor has exceeded the periosteum with frozen sections during surgery (27-31). Orbital exenteration does not have a positive effect on survival in patients with advanced paranasal sinus cancer, but recurrence in orbita is considered to be an important poor prognostic factor (27-29,31). Nevertheless, as in most head and neck cancers, preservation of the orbita by periostal resection is considered an appropriate approach since it can provide a functional eye and provide a comparable survival advantage in case of incomplete periostal invasion (27-29,31). With all these data, orbital exenteration is considered as an appropriate approach in patients with orbital invasion and paranasal sinus malignancies that significantly exceed periorbital (27-31).

Technological advances have enabled the treatment of paranasal sinus tumors with imaging-guided endoscopic resections. In studies, open or endoscopic tumor resection has similar results in terms of obtaining
sufficient surgical margins. In addition to curative treatment, endoscopic sinus surgery may be preferred for palliation of symptoms such as nasal obstruction and epistaxis in paranasal sinus cancers (25,26).

Cervical lymph node metastasis is rare in paranasal sinus and nasal cavity cancers. In a study in which 74 patients with paranasal sinus cancer were followed for more than 25 years, the incidence of cervical lymph node metastasis was 14% at the time of diagnosis or within 5 years of diagnosis (9,32). Neck dissection and subsequent radiation therapy are recommended in all patients with cervical lymph node involvement. However, prophylactic approach with neck dissection or radiotherapy in N0 disease without lymph node metastasis is controversial (9). However; ipsilateral prophylactic neck dissection should be recommended in T3 and T4 cases (9,32,33).

7. Systemic medical treatment

There is no optimal and clear consensus on the use of systemic anti-cancer drugs within the multimodal approach before or after surgery and/or radiotherapy in the treatment of paranasal sinus and nasal cavity cancers. In the literature, it can be added to curative radiation therapy in patients with paranasal sinus and nasal cavity cancer who cannot be resected surgically or can be applied concurrently with adjuvant radiotherapy in patients with poor prognostic features such as positive surgical margin or extracapsular spread after surgical resection (34-40).

In a prospective study by Licitra et al. (41), 49 patients with paranasal sinus cancer, 38 of whom had T3 or T4 tumors, who had no prior treatment and were resectable, have been evaluated. In this study, 19 of the 21 patients who responded after cisplatin-based chemotherapy and 23 of the 28 patients who had no response were treated with surgical and post-operative radiotherapy; the 3-year overall survival rate was reported to be 69% (41). In a study of 39 patients with stage IVB disease who did not undergo surgical resection, 35 patients were treated with curative radiotherapy plus chemotherapy and 4 patients with curative radiotherapy alone. It was reported that 5-year disease-free survival and overall survival rates were approximately 15% for these patients who were followed for over an average 7 years (42).

In a study comparing postoperative adjuvant radiation therapy or concomitant chemo-radiotherapy versus patients who received only concurrent chemo-radiotherapy, the mean progression-free survival was 45 months and the overall survival rate was 65%. It was emphasized that better survival results were achieved in patients who underwent surgery with this study, which included patients with follow-up over an average 6 years (43).
Hanna et al. (43) compared 46 patients who underwent surgery and adjuvant radiotherapy after induction chemotherapy and 22 patients treated with concomitant chemo-radiotherapy. In this study, 67% of all patients had partial or complete response, 9% had stable disease and 24% had progressive disease. The 2-year survival rate of patients who responded to induction chemotherapy was found to be 77%, while this rate was reported to be 36% in patients with progression to induction chemotherapy (44).

In a retrospective study of 179 patients, most of whom had T4N0 disease; induction chemotherapy did not provide significant difference in terms of overall survival results from concomitant high-dose cisplatin and radiotherapy (45).

There is no data in the literature that may differ from other head and neck malignancies in the treatment of patients with metastatic paranasal sinus and nasal cavity cancer (42,46). It is recommended that the anti-cancer drugs to be given in metastatic disease be selected according to the histological type of cancers of the paranasal sinus and nasal cavity. In patients with locally advanced or metastatic squamous cell paranasal sinus and nasal cavity cancer, cisplatin-fluorouracil-cetuximab combination therapy, which is used in metastatic treatment of patients with squamous head and neck cancer other than nasopharyngeal cancer, may be preferred (47).

The prognostic value of PD-L1 positivity in paranasal sinus and nasal cavity cancers is not clear (48). However, it has been reported that promising rates of benefit may be achieved with immune check point inhibitors in metastatic patients (48).

8. Conclusion

When the literature information is reviewed, it is seen that the clinical and treatment characteristics of paranasal sinus and nasal cavity cancers are not clear and that there is no positive development regarding current targeted therapies and immunotherapy options. Because of the rarity of cancers, there is no clear consensus because of the inadequacy of randomized clinical trials based on optimal and standard treatment in terms of surgery, radiation therapy and systemic drug therapies. It may be concluded that new studies are needed for the molecular basis of these cancers, their carcinogenesis characteristics and treatment options.
References


<table>
<thead>
<tr>
<th>Tumor Localization</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
</table>
| Maxillary sinus    | Tx Primary tumor could not be evaluated  
Tis Carcinoma in situ  
T1 Primary tumor limited to maxillary sinus mucosa without evidence of bone erosion or invasion  
T2 Primary tumor causing bone erosion or destruction involving extension into the middle nasal meatus and/or hard palate, excluding extension to the posterior wall of the maxillary sinus and pterygoid plaques  
T3 Primary tumor invading any of the posterior wall of the maxillary sinus, subcutaneous tissues, orbital floor or lateral wall, pterygoid fossa, ethmoid sinuses  
T4a Moderately advanced local disease; Primary tumor invading the anterior orbital structures, cheek skin, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses  
T4b Highly advanced local disease; Primary tumor invading any of the orbital apex, dura, brain, middle cranial fossa, cranial nerves other than the maxillary | Nx Regional lymph node could not be evaluated  
N0 No regional lymph node involvement  
N1 Ipsilateral metastasis in a single lymph node with a maximum diameter of cm3 cm and no extranodal spread  
N2a Ipsilateral metastasis in a single lymph node with a maximum diameter> 3 cm but ancak6 cm and no extranodal spread  
N2b Metastasis in ipsilateral multiple lymph nodes with a maximum diameter> 6 cm and no extranodal spread  
N2c Ipsilateral or contralateral lymph node metastases with a maximum diameter> 6 cm and no extranodal spread  
N3a Lymph node metastasis with the largest diameter> 6 cm and without extranodal spread  
N3b Metastasis of any lymph node or lymph nodes with clinically | M0 No distant metastasis  
M1 distant metastasis |
<table>
<thead>
<tr>
<th>Ethmoid sinus and nasal cavity</th>
<th>portion of the trigeminal nerve (V2), nasopharynx or clivus</th>
<th>significant extranodal spread</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tx</strong> Primary tumor could not be evaluated</td>
<td><strong>Nx</strong> Regional lymph node could not be evaluated</td>
<td><strong>M0</strong> No distant metastasis</td>
</tr>
<tr>
<td><strong>Tis</strong> Carcinoma in situ</td>
<td><strong>N0</strong> No regional lymph node involvement</td>
<td><strong>M1</strong> distant metastasis</td>
</tr>
<tr>
<td><strong>T1</strong> Primary tumor confined to any background, with or without bone invasion</td>
<td><strong>N1</strong> Ipsilateral metastasis in a single lymph node with a maximum diameter of cm3 cm and no extranodal spread</td>
<td></td>
</tr>
<tr>
<td><strong>T2</strong> Primary tumor with or without bone invasion involving one of the additional structures within the nasoethmoidal complex or invading two infrastructures in a single site</td>
<td><strong>N2a</strong> Ipsilateral metastasis in a single lymph node with a maximum diameter&gt; 3 cm but &lt;6 cm and no extranodal spread</td>
<td></td>
</tr>
<tr>
<td><strong>T3</strong> Primary tumor invading the medial wall or base of the orbit, maxillary sinus, palate or cribiform plate</td>
<td><strong>N2b</strong> Metastasis in ipsilateral multiple lymph nodes with a maximum diameter&gt; 6 cm and no extranodal spread</td>
<td></td>
</tr>
<tr>
<td><strong>T4a</strong> Moderately advanced local disease; Primary tumor invading any of the anterior orbital structures, cheek or nose skin, anterior cranial fossa with minimal spread, pterygoid plates, sphenoid or frontal sinuses</td>
<td><strong>N2c</strong> Ipsilateral or contralateral lymph node metastases with a maximum diameter&gt; 6 cm and no extranodal spread</td>
<td></td>
</tr>
<tr>
<td><strong>T4b</strong> Highly advanced local disease; Primary tumor invading any of the orbital apex, dura, brain, middle cranial fossa, cranial nerves other than the maxillary portion of the trigeminal nerve (V2), nasopharynx, or clivus</td>
<td><strong>N3a</strong> Lymph node metastasis with the largest diameter&gt; 6 cm and without extranodal spread</td>
<td></td>
</tr>
<tr>
<td><strong>N3b</strong> Metastasis of any lymph node or lymph nodes with clinically significant extranodal spread</td>
<td></td>
<td></td>
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Table 2. Tumor (T), Nod (N), Metastasis (M) (TNM) staging system for paranasal sinuses and nasal cavity malignencies designed by the American Joint Committee on Cancer (AJCC) in 2017

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1, T2, T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1, T2, T3, T4a</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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</tbody>
</table>

Table 3. Treatment recommendations according to tumor localization and disease stage for paranasal sinuses and nasal cavity malignancies

<table>
<thead>
<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxill ary Sinus Cancer s</td>
<td>Surgical resection with high-dose, curative pre- or post-operative radiotherapy</td>
<td>Surgical resection with high-dose, curative pre- or post-operative radiotherapy</td>
<td>Superfractionated pre- or post-operative radiation therapy</td>
<td>It includes locally advanced lesions and the standard treatment of choice is high-dose definitive radiotherapy for these lesions</td>
</tr>
<tr>
<td>Infraestructure, small, mucosal lesions</td>
<td>Post-operative radiotherapy in the presence of close surgical margins, especially in suprastructural tumors</td>
<td>Radiation therapy is under clinical evaluation</td>
<td>It has been reported that this treatment option is contraindicated in surgery and is a potential treatment in patients with nasopharyngeal and skull base spread</td>
<td>Craniofacial resection with post-operative radiation therapy or post-operative radiotherapy</td>
</tr>
<tr>
<td>Primary treatment is surgical resection</td>
<td></td>
<td></td>
<td></td>
<td>Craniofacial resection after radiation therapy if indicated</td>
</tr>
<tr>
<td>Post-operative radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td>Chemothrapy should be recommended in case of inadequate treatment after the first two recommendations</td>
</tr>
<tr>
<td><strong>Ethmoid Sinus Cancers</strong></td>
<td>Tumors with extension usually at the time of diagnosis</td>
<td>Tumors with extension usually at the time of diagnosis</td>
<td>Surgical resection with craniofacial approach, usually combined with post-operative radiation therapy, is recommended</td>
<td></td>
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<td>--------------------------</td>
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<td>------------------------------------------------------</td>
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<tr>
<td>Non-resectable tumors usually require external radiation therapy alone</td>
<td>Non-resectable tumors usually require external radiation therapy alone</td>
<td>Clinical trials involving new drug combination(s) with the aim of applying chemotherapy prior to surgery or radiotherapy are under</td>
<td>Surgical resection involving craniofacial resection in combination with pre- or post-operative radiation therapy for those lesions that involve locally advanced lesions and the choice of standard treatment</td>
<td></td>
</tr>
<tr>
<td>Good and limited localized tumors can be surgically resected. However, it usually requires a</td>
<td>Good and limited localized tumors can be surgically resected. However, it usually requires a</td>
<td>Simultaneous chemotherapy and radiotherapy is a treatment option for non-operable</td>
<td>Radiation therapy or craniofacial resection after limited surgery or both may be recommended</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Craniofacial resection after radiation therapy</td>
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<td></td>
<td></td>
<td></td>
<td>Chemotherapy should be recommended in case of inadequate treatment after the first two recommendations</td>
<td></td>
</tr>
<tr>
<td><strong>Sphenoid Sinus Cancer</strong>s</td>
<td>Craniofacial approach including resection of the ethmoid, maxilla and orbit</td>
<td>Craniofacial approach including resection of the ethmoid, maxilla and orbit</td>
<td>Evaluation in advanced tumors and should be considered as recommendations</td>
<td><strong>Nasal Cavity Cancer</strong>s</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Sphenoid Sinus Cancer</strong>s</td>
<td>Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers</td>
<td>Standard treatment offer is primarily radiotherapy as in nasopharyngeal cancers</td>
<td>Simultaneous chemoradiotherapy may also be recommended</td>
<td><strong>Sphenoid Sinus Cancer</strong>s</td>
</tr>
<tr>
<td><strong>Nasal Cavity Cancer</strong>s</td>
<td>Treatment options for squamous cell carcinoma are either surgical or radiation</td>
<td>Treatment options for squamous cell carcinoma are either surgical or radiation</td>
<td>Standard treatment recommendation is surgery alone, radiotherapy alone, chemotherapy</td>
<td><strong>Nasal Cavity Cancer</strong>s</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Clinical trials involving new chemotherap y agents should be evaluated</strong></td>
</tr>
<tr>
<td>Therapy because they have similar cure rates</td>
<td>Combined surgery and radiation therapy (recommended adjuvant radiation therapy)</td>
<td>Combined surgery and radiation therapy (recommended adjuvant radiation therapy)</td>
<td>Treatment of approximately 25% of patients</td>
<td></td>
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<tr>
<td>Standard treatment is surgery for septum tumors, but for lateral and superior wall tumors, this treatment is radiation therapy, and for septal and lateral wall tumors surgery and adjuvant radiotherapy</td>
<td>Concurrent chemo-radiotherapy may be recommended in eligible patients</td>
<td>Concurrent chemo-radiotherapy may be recommended in eligible patients</td>
<td>Craniofacial resection is recommended in patients with relapse after radiotherapy, and radiation therapy in patients with recurrence after surgery should be recommended</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy should be recommended after clinical trials involving new drug combinations, as well as surgical or combined-modality therapies for pre-operative or radiation therapy</td>
<td>Adjuvant chemotherapy should be recommended after clinical trials involving new drug combinations, as well as surgical or combined-modality therapies for pre-operative or radiation therapy</td>
<td>Adjuvant chemotherapy should be recommended after clinical trials involving new drug combinations, as well as surgical or combined-modality therapies for pre-operative or radiation therapy</td>
<td>Chemotherapy should be recommended in case of inadequate treatment after the first two recommendations</td>
<td></td>
</tr>
<tr>
<td>Clinical trials involving new chemotherapy agents should be evaluated</td>
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