REVIEW ARTICLE

Maxillary Sinus Squamous Cell Carcinoma: Clinical Perspectives and Advancing Therapeutics Across Disease Stages

Mythileeswari Lakshmikanthan[1], Varadareddygari Venugopal Reddy[2], Touzeen Hussain[3], Megala Sivaprakasam[4], Vijayaraj Radha[5], Shenbhagaraman Ramalingam[6], Mukesh Kumar Dharmalingam Jothinathan[7], Archana Behera[7], Sakthivel Muthu[8]

[1]Department of Research, Saveetha College of Nursing, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [2]Department of General Medicine, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [3]Department of General Surgery, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India, [4]Department of Microbiology, St. Joseph's College of Arts and Science (Autonomous), Cuddalore, Tamil Nadu, India, [5]Department of Marine Biotechnology, AMET UNIVERSITY, Chennai, Tamil Nadu, India, [6]Department of ENT, Saveetha Medical College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, [7]Department of Biochemistry, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India, [8]Department of Dermatology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India

Abstract

Squamous cell carcinoma (SCC) of the maxillary sinus is a rare but very aggressive cancer in the paranasal sinus area. Clinical outcomes are mostly affected by tumor stage diagnosis, histopathological features, and patient-related factors. Early-stage tumors (T1, T2) usually respond good to combined treatment while advanced lesions (T3, T4) show wide local invasion, reduced survival, and more chance of recurrence. This review discusses important prognostic factors, treatment options, and changes in the management of maxillary sinus SCC. Variable such as lymph node status, tumor differentiation, invasion depth, and molecular marker was considered. Treatment strategies were analyzed according to tumor spread, risk of relapse, and patient condition. Surgical resection with curative aim remains the main treatment, especially for tumor limited to the maxillary sinus. In patients with high-risk features, adjuvant radiotherapy is often used to reduce local failure. For advanced or recurrent disease, systemic therapy like platinum-based chemotherapy such as cisplatin and 5-fluorouracil is commonly used. Target therapy including epidermal growth factor receptor inhibitor cetuximab and immune therapy like pembrolizumab and nivolumab also shows benefit in some patients. However, the long-term outcome still depends mostly on the stage at diagnosis. Even with improvement in treatment, the management of maxillary SCC still faces many problems, mainly with late-stage disease. More studies on molecular target drugs and immune-based treatment may help to improve survival in patients with aggressive or treatment-resistant tumors.

Key words: Chemoradiation, immunotherapy, prognosis, recurrence, treatment

Address for correspondence:
Sakthivel Muthu, Department of Dermatology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences, Thandalam, Chennai - 602105, Tamil Nadu, India.
E-mail: saktthivel@gmail.com

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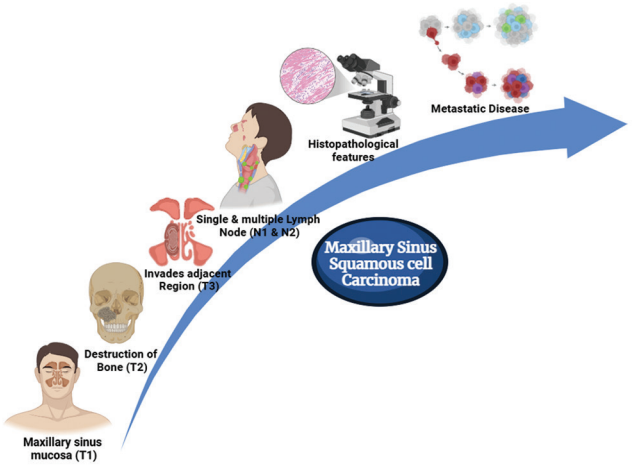
GRAPHICAL ABSTRACT



INTRODUCTION

Maxillary sinus cancer, although rare, is a serious and difficult malignancy to manage. It accounts for about 0.2% of all human tumors and nearly 1.5% of head-and-neck cancer. Even though it is the most common type of paranasal sinus carcinoma with nearly 80% arising from the maxillary sinus, the overall incidence is still low worldwide.[1,2] Some region specially Asia shows a higher incidence rate which indicates the need for more awareness among healthcare workers, especially oral stomatologists.[3,4] This awareness is important for early diagnosis and better disease control.

Squamous cell carcinoma (SCC) of the maxillary sinus also called maxillary sinus squamous cell carcinoma (MxSSCC) is the most frequent malignancy in this site. It mainly affects middle-aged male patients, usually between 55 and 65 years. The cause of MxSSCC is related to many environmental factors, such as long-term exposure to chemical agents, tobacco smoke, and viral infection such as human papilloma virus (HPV). These factors play a role in tumor development and stress the importance of identifying high-risk individuals in clinical as well as epidemiological practice.[5]

One major problem in the diagnosis of maxillary sinus cancer is that the early symptom is vague and non-specific. Initial complaint such as nasal blockage, facial pain, or sinus discharge is often confused with simple sinusitis or infection. Because of this, many patients are diagnosed at a late stage. Nearly 70–80% of cases already show local spread at the time of diagnosis involving the bone, skull base, or orbit. Late detection also makes it difficult to identify the exact origin of the tumor which complicates treatment planning and prognosis.[6,7] Moreover, advanced disease stage led to poor prognosis due to aggressive invasion of vital structures, increasing treatment difficulty, and recurrence rate.[8,9]

For diagnosis, imaging techniques are very important. Computed tomography (CT) is the most commonly used imaging method giving information about tumor size, site, and extension to nearby tissue.[10,11] CT scan has been used since the 1980s, especially in Japan, and plays a key role in staging and evaluation of bone involvement. Magnetic resonance imaging and positron emission tomography scans may also be used in selected patients to assess further spread.

Management of maxillary sinus cancer requires a multidisciplinary approach. Surgery is the mainstay of treatment and when combined with radiotherapy, survival outcomes improve significantly. However, surgery is difficult because of the complex anatomy of the maxillary sinus and close relation to the orbit, skull base, and other vital structures.[12,13] Craniofacial resection introduced in 1960s changed surgical management by allowing the removal of large and complex tumors with an acceptable margin. Still, this surgery carries high risk such as bleeding, nerve injury, and long-term functional deficit. To overcome this problem, reconstructive methods have improved over time. Free flap reconstruction becomes a major advance, helping restore both form and function after extensive resection. These techniques improve recovery, reduce complications, and enhance quality of life. Yet, craniofacial surgery remains technically demanding and requires an experienced surgical team.[7,14] Besides treatment, prognostic factors are very important in predicting outcome. Tumor size, stage involvement of adjacent structures, and patient general health all affect survival and treatment response. Ongoing research focuses on identifying prognostic markers to improve treatment planning and individualized care for patients with MxSSCC. In conclusion, maxillary sinus cancer is a rare and difficult-to-diagnose malignancy. Progress in imaging surgery and reconstruction has improved patient outcomes, but late presentation and technical challenges still exist. There is a need for more research, better awareness, and improved diagnostic approach. Understanding prognostic factors is essential to optimize management and improve the survival of patients with this disease.

ETIOLOGY OF MxSSCC

MxSSCC is a malignant tumor that mainly arises from the maxillary sinus, a large, paired cavity present in the facial bone [Figure 1]. The exact cause is not a single but complex and multifactorial. Several contributing factors have been reported for the development of MxSSCC.[15] These factors include:

Tobacco use

Tobacco use is one of the most important risk factors for SCC in the head-and-neck area including the maxillary sinus.[16,17] Smoking causes cancer by inhalation of toxic chemicals and carcinogens present in tobacco smoke which

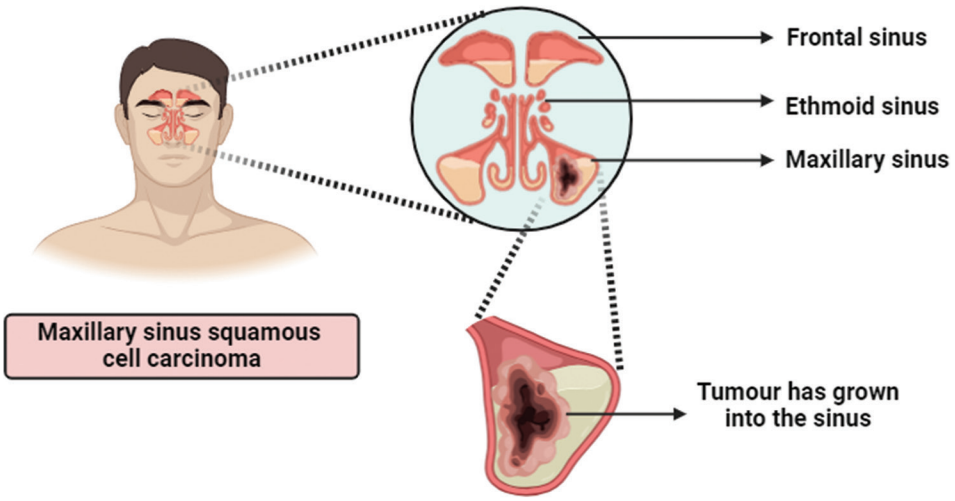


Figure 1: The maxillary sinus impacted by squamous cell carcinoma

lead to abnormal change of epithelial cell lining of the sinus. Long-term and cumulative exposure increases the chance of malignant change significantly.[18]

Alcohol consumption

Excess alcohol intake specially when associated with tobacco use further increases the risk of *SCC* of the maxillary sinus and other head-and-neck regions.[19,20] Alcohol acts as an irritant to the mucosa causing chronic inflammation, epithelial damage, and an increased possibility of malignant transformation over time.[21,22]

Occupational exposures

Some occupations expose workers to carcinogenic substances that raise the risk of MxSSCC. Jobs related to wood dust, textile industry, metal work, and leather processing show a higher incidence of sinonasal cancer.[23] Continuous exposure to airborne particles and chemicals leads to chronic irritation of the sinus mucosa and promotes tuVmor formation.[24,25]

Viral infections

Viral infection, especially HPV, has been linked with many head-and-neck cancers including MxSSCC.[26,27] High-risk HPV strains such as HPV 16 and HPV 18 may induce epithelial cell transformation in the maxillary sinus, leading to carcinogenesis. Although HPV-related SCC usually shows a better prognosis, the exact role of HPV in MxSSCC is still under investigation.[28,29]

Chronic inflammation and irritation

Chronic inflammation of the maxillary sinus due to long-standing sinusitis can result in squamous metaplasia. This condition involves the replacement of normal respiratory epithelium by squamous cells, increasing the risk of malignant change. Persistent irritation from allergic rhinitis, nasal polyps, or repeated infection creates a favorable environment for tumor development.[30,31]

Genetic predisposition

Genetic factors may contribute to the development of MxSSCC, especially in patients with a positive family history of cancer. Specific genes responsible are not clearly identified yet. Some studies suggest inherited mutation may predispose an individual to squamous metaplasia and later carcinoma.[32,33] Mutation of p53 tumor suppressor gene which regulates the cell cycle and prevents uncontrolled growth has been reported in several head and neck *SCC* including maxillary sinus cancer.[34,35]

CLINICOPATHOLOGICAL CHARACTERISTICS OF MxSSCC

The development of MxSSCC usually occurs through series of pathological changes, starting from normal epithelium to squamous metaplasia, then dysplasia, and finally carcinoma. It is important to mention that studies related to MxSSCC stress the use of proper inclusion and exclusion criteria when describing clinicopathological features and symptoms of disease.[36] These criteria help in the correct diagnosis and in distinguishing benign from malignant lesions, which allows better prediction of prognosis and planning of treatment [Figure 2]. The association between chronic sinusitis and development of squamous metaplasia in sinus epithelium is an important factor in understanding the cause of this carcinoma. Long-standing inflammation may alter the normal epithelial lining and create conditions favorable for malignant transformation.[37]

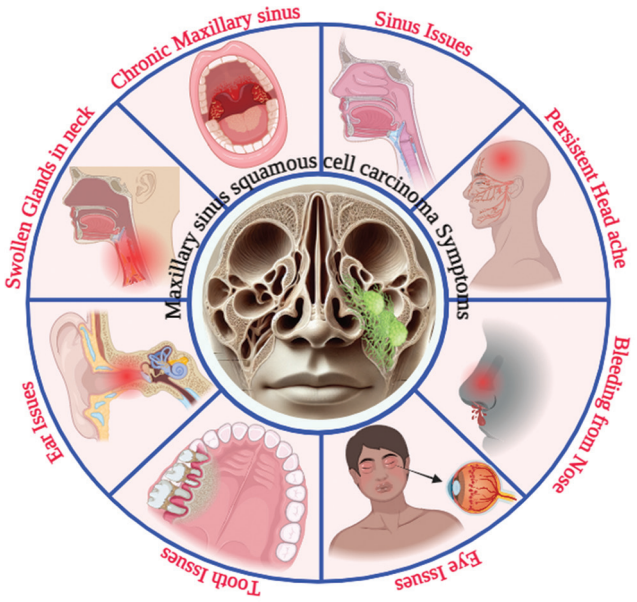


Figure 2: The clinical symptoms associated with squamous cell carcinoma of the maxillary sinus

PROGNOSIS OF MxSSCC

The prognosis of patients with MxSSCC depends on many clinical, pathological, and molecular factors. Understanding this factor is very important for selecting a proper treatment strategy and estimating survival outcomes. The main elements that influence prognosis include tumor stage, histopathological features, and the patient's general health condition and personal characteristics.[38]

TUMOR STAGE AND LOCAL INVASION

Early stage (T1, T2)

Tumors limited to the maxillary sinus (T1 and T2) usually show a better prognosis. These lesions are localized and often suitable for surgical removal. When surgery is combined with proper adjuvant therapy, the treatment outcome becomes more favorable. Early diagnosis and timely treatment play a major role in improving the survival rate.[39-41]

Advanced stage (T3, T4)

Advanced stage tumors (T3 and T4) are marked by extensive local invasion into nearby tissue such as bone, orbit, and skull base. As tumors extend to deeper structures, treatment becomes more complex and overall survival rate declines. Patients with advanced disease often need aggressive management including combined surgery, radiotherapy, and chemotherapy.[42,43]

LYMPH NODE INVOLVEMENT

Lymph node metastasis is a very important prognostic factor in MxSSCC. The presence of an enlarged lymph node, especially classified as N1 or N2, is linked with poor prognosis because it shows tumor spread beyond the primary site. Lymph node involvement can markedly decrease the survival rate and make treatment options more difficult. The size, number, and extent of the involved node are key elements in assessing metastatic risk and in deciding an appropriate treatment plan.[44]

HISTOPATHOLOGICAL FEATURES

Tumor differentiation

Well-differentiated tumors show keratin formation and low mitotic activity and usually have a better prognosis. These tumors grow slowly and are less aggressive toward surrounding tissue. On the other hand, poorly differentiated tumors behave more aggressively and show a higher chance of metastasis and recurrence.[45,46]

Perineural invasion (PNI)

PNI, where tumors spread along nerves, is considered an important negative prognostic factor. This feature suggests a possible extension of cancer through the nerve pathway, making complete surgical removal difficult and increasing the risk of local recurrence.[47,48]

Lymphovascular invasion (LVI)

LVI occurs when tumor cells infiltrate blood vessels or lymphatic channels. This condition increases the risk of regional and distant metastasis and is usually associated with a poor prognosis.[49,50]

Necrosis and mitotic activity

Tumor necrosis is commonly seen in poorly differentiated lesions and, along with high mitotic rate, indicates aggressive tumor behavior. Such tumors tend to grow fast and are more likely to invade adjacent structures and lymph nodes.[51,52]

MOLECULAR MARKERS

Molecular markers such as mutation of p53 tumor suppressor gene and presence of HPV infection give important prognostic information in MxSSCC. HPV-related tumors, especially those positive for p16INK4a which is a marker of HPV-induced carcinogenesis, usually show

better prognosis because they respond better to treatment. In contrast, p53 mutations are linked with poor outcomes since they indicate loss of tumor suppressive function, leading to uncontrolled cell division, tumor growth, and disease progression.[35,53]

TREATMENT OUTCOMES AND SURVIVAL

Surgical resection

Surgical resections remain the main treatment option for MxSSCC and obtaining a clear surgical margin is very important for survival improvement. Complete excision of tumor without residual malignant tissue decreases the chance of recurrence and helps in achieving better long-term outcomes.[54,55]

Adjuvant therapies

In cases with high-risk features, additional treatment such as radiotherapy or chemotherapy is frequently used to manage residual disease or possible regional and distant metastasis. These therapies are especially necessary in advanced-stage tumors where surgery alone is often not enough.[2,56,57]

Age and patient factors

Patient age also influences prognosis. Younger patients generally show better outcomes compared to older patients because they can tolerate aggressive treatment and recover more effectively. In addition, biomarkers like p16INK4a are now considered useful prognostic indicators, and higher expression is associated with improved treatment response and survival.[58,59]

TUMOR METASTASIS AND CRITICAL STRUCTURE INVOLVEMENT

Involvement of critical structures like orbit or skull base makes treatment more difficult and worsens prognosis. These areas are hard to treat by surgery and their close relation to vital organs increases the risk of functional problems and life-threatening complications. Tumor spread, especially to distant organs, reduces treatment effectiveness and lower survival rate [Table 1]. In summary, the prognosis of MxSSCC mostly depends on tumor stage, histopathological features, lymph node involvement, and molecular markers. Early-stage tumors generally show a much better prognosis, while advanced tumors with local invasion or metastasis need more aggressive treatment and have a poor outcome. Achieving a clear surgical margin and using adjuvant therapy together with consideration of patient factors remain important to improve survival in patients with MxSSCC.[57,60]

Table 1: Prognosis and treatment outcomes for squamous cell carcinoma of the maxillary sinus

Key prognostic factors	Involvement	References
Tumor stages		
T stages	TX (Primary tumor)	[1]
	Tis (Carcinoma *in situ*)	[2]
	T1 (Maxillary sinus mucosa)	[3]
	T2 (Destruction of bone)	[4]
	T3 (Invades adjacent region)	[5]
	T4a (Moderately advanced)	[6]
	T4b (Very advanced)	[7]
N stages	N1 (Single lymph node)	[8]
	N2 (Multiple nodes)	[9]
Histopathological features	Differentiation	[10]
	Depth of invasion	[5]
	Keratinization	[11]
	Mitotic rate	[12]
	Necrosis	[13]
	Cellular atypia	[14]
	Inflammatory response	[15]
	Molecular markers	[16]
Metastatic disease	Patterns of spread	[1]
	Clinical impact	[3]
	Diagnosis and monitoring	[17]
	Management	[1]
	Prognosis	[18]
Patient factors	Age	[19]
	Gender	[1]
Treatment modality		
Surgical resection	Primary treatment	[3]
Adjuvant therapy	Radiotherapy	[20]
Tumor location	Orbit or cranial cavity	[21]
Biomarkers and molecular factors	p16INK4a, HPV status	[22]

TREATMENT OF MxSSCC

MxSSCC is a rare but aggressive malignancy originating in the maxillary sinus, a paranasal sinus located within the facial skeleton. The therapeutic management of MxSSCC generally involves multidisciplinary approach that combines surgery, radiation therapy, and systemic treatments, depending on the stage and extent of the disease. Early-stage cancers typically have better outcomes, but advanced-stage cases present

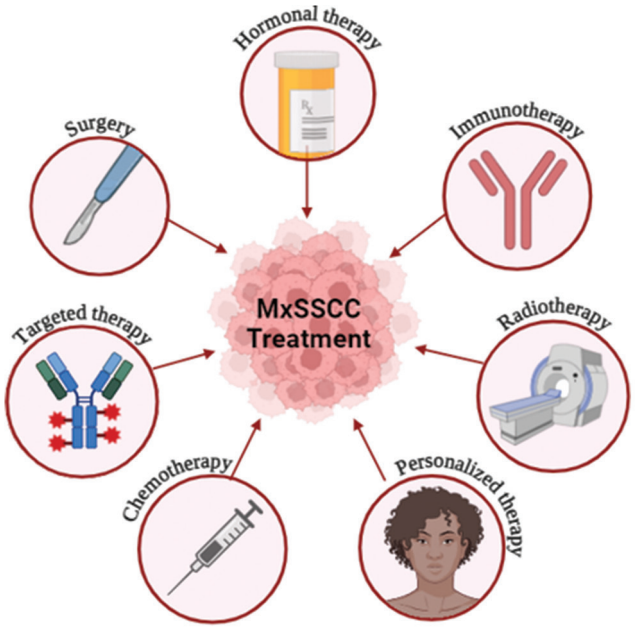


Figure 3: The different therapeutic strategies for managing maxillary sinus squamous cell carcinoma

more significant challenges in terms of treatment, functional preservation, and survival [Figure 3].[61,62]

Surgical resection

Surgical resection is the cornerstone of treatment for MxSSCC, aiming to achieve complete tumor excision while maintaining functional integrity. For early-stage tumors (T1 and T2), surgical treatment is often successful, with minimal recurrence and an excellent survival rate. The goal is to remove the tumor with clear margins to prevent the risk of local recurrence [Table 1].[8,63] In advanced-stage tumors (T3, T4), surgery becomes more complex due to local invasion into adjacent structures such as the orbit, skull base, and surrounding soft tissues. This often necessitates more extensive surgical procedures including maxillectomy (removal of part or all of the maxilla) and craniofacial resection to achieve adequate tumor clearance.[64] Unfortunately, these aggressive surgeries can lead to significant functional and esthetic complications including facial disfigurement, speech or swallowing difficulties, and impaired vision if the orbit is involved. Despite efforts for clear margins, advanced tumors often present a challenge in ensuring complete tumor excision, and surgical resection in these cases is associated with higher rates of positive margins and recurrence. For these reasons, the prognosis for advanced-stage disease tends to be less favorable, and post-operative adjuvant therapies are often employed to control residual disease and reduce recurrence risk.[57]

Radiation therapy

Radiation therapy is frequently used as an adjuvant to surgery, particularly when tumor involves critical areas where complete resection is not feasible or when surgical margins are compromised. Radiation plays a pivotal role in improving local control, reducing the risk of recurrence, and addressing any microscopic disease left behind after surgery. It is especially valuable when surgery is contraindicated due to tumor location or patient's medical condition.[55] However, radiation therapy carries its own set of challenges and side effects, such as mucositis (inflammation of mucous membranes), osteoradionecrosis (damage to bone tissue caused by radiation), and long-term xerostomia (dry mouth). These side effects can significantly impact a patient's quality of life, and managing them requires careful monitoring and supportive care. In cases where surgery alone is insufficient or not possible due to tumor location, radiation therapy can be combined with chemotherapy or chemoradiation to improve outcomes. Chemoradiation, concurrent use of chemotherapy and radiation therapy, is often used for locally advanced or inoperable tumors. This approach has shown improved locoregional control and survival rates compared to radiation therapy alone, although it comes with increased toxicity including heightened risk for mucositis, skin ulceration, and esophagitis.[65,66]

Chemotherapy

Chemotherapy plays a significant role in the treatment of advanced or metastatic MxSSCC. Platinum-based agents, particularly cisplatin, are commonly used in combination with radiation for locally advanced head-and-neck cancers, including MxSSCC. Cisplatin interferes with DNA replication, leading to cell death and enhanced radiosensitivity. Carboplatin, less toxic alternative to cisplatin, may also be used, particularly in patients who cannot tolerate cisplatin side effects. Other chemotherapy agents used in combination regimens include 5-fluorouracil (5-FU), an antimetabolite that inhibits DNA synthesis and is often employed along with cisplatin for a synergistic effect. Taxanes such as docetaxel and paclitaxel are also used in combination therapies for advanced MxSSCC due to their ability to stabilize microtubules, preventing cell division and promoting tumor cell death.[67,68]

Targeted therapies

Targeted therapies, particularly those aimed at specific molecular markers, represent a promising avenue in the treatment of advanced or recurrent MxSSCC. One of the most well-established targeted therapies in head-and-neck cancers is cetuximab (Erbitux), a monoclonal antibody that targets epidermal growth factor receptor (EGFR). EGFR is overexpressed in many head-and-neck cancers including MxSSCC, and targeting this receptor with cetuximab has been shown to improve outcomes when used in combination with chemotherapy or radiation therapy. Cetuximab blocks the EGFR signaling pathway, which is involved in tumor

cell proliferation and survival. Other EGFR inhibitors, such as erlotinib (Tarceva) and gefitinib (Iressa), may also be used in recurrent or metastatic MxSSCC. These drugs work by inhibiting EGFR activity, thus reducing tumor cell proliferation and enhancing the effects of radiation and chemotherapy.[69,70]

Immunotherapy

In recent years, immunotherapy has become an important treatment option for patients with advanced or recurrent MxSSCC, particularly those with high levels of PD-L1 expression.[71,72] Immunotherapy agents such as pembrolizumab (Keytruda) and nivolumab (Opdivo), both PD-1 inhibitors, work by blocking the interaction between PD-1 on immune cells and PD-L1 on tumor cells, allowing the immune system to better recognize and attack cancer cells. These agents have shown significant efficacy in treating recurrent or metastatic head-and-neck SCC, particularly when tumor cells express high levels of PD-L1. In addition, atezolizumab (Tecentriq), a PD-L1 inhibitor, is under investigation for its role in treating recurrent or metastatic MxSSCC, offering hope for patients who have exhausted other treatment options. Immunotherapy is often used in combination with other treatment modalities such as chemotherapy and radiation, especially in cases where tumors are resistant to traditional therapies.[73]

Supportive care

Supportive care plays a critical role in managing the side effects of aggressive cancer treatments. Drugs such as antiemetics (e.g., ondansetron and metoclopramide) are used to manage chemotherapy-induced nausea and vomiting, while analgesics (e.g., acetaminophen and NSAIDs) help manage pain.[74] Growth factors such as granulocyte colony-stimulating factors and filgrastim are administered to stimulate white blood cell production, reducing the risk of infections during chemotherapy. As the landscape of MxSSCC treatment continues to evolve, combination therapies are becoming increasingly common.[75,76] For example, a combination of cisplatin and 5-FU remains the standard approach for advanced SCC, while cetuximab combined with radiation is a valuable strategy for locally advanced cases.[77] Furthermore, the use of pembrolizumab in combination with chemotherapy is under investigation, with early studies suggesting promising results in improving survival for patients with recurrent or metastatic MxSSCC.[78,79]

PROGNOSIS AND TREATMENT OUTCOMES

The prognosis for patients with MxSSCC is highly dependent on stage at diagnosis, extent of tumor, and treatment approach. Early-stage (I-II) tumors generally have a more favorable prognosis, with 5-year survival rates ranging 25–50%. Advanced-stage (III-IV) cases, particularly those with local invasion or metastasis, experience poorer outcomes, with survival rates ranging from 20% to 50%. Recurrence is a significant challenge, particularly in the first 2–3 years following treatment, especially for advanced-stage disease. Even with aggressive treatment, local recurrence and distant metastasis remain common, underscoring the need for long-term follow-up and surveillance.[38,43]

Emerging therapies, including immunotherapy and molecularly targeted treatments, are being actively explored for their potential role in managing advanced or recurrent MxSSCC. Although their efficacy is still being evaluated in clinical trials, these therapies offer hope for improving outcomes in this difficult-to-treat malignancy. In conclusion, treatment of MxSSCC requires a comprehensive, multidisciplinary approach, including surgery, radiation, chemotherapy, and emerging targeted therapies. While early-stage tumors generally offer better prognosis, advanced-stage cases pose significant treatment challenges, necessitate innovative approaches to improve patient outcomes, and minimize recurrence.[72,80]

CONCLUSION

MxSSCC presents a significant therapeutic challenge due to its varied prognosis, influenced by tumor stage, histopathological characteristics, and patient factors. Early-stage tumors typically have better outcomes following surgical resection while advanced cases necessitate more extensive procedures, leading to increased recurrence and poorer survival rates. Treatment strategies involve multimodal approach, including surgery, radiation therapy, and systemic therapies such as chemotherapy and targeted agents. Chemotherapy regimens commonly utilize cisplatin and 5-FU while immunotherapy has gained traction as a vital option for advanced cases, especially with agents like pembrolizumab and nivolumab. Despite advancement, patients face significant long-term sequelae, highlighting the need for ongoing research into emerging therapies and the importance of individualized treatment plans to optimize outcomes in this rare malignancy.

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AUTHOR CONTRIBUTIONS

Conceptualization, Data curation, Visualization, Formal analysis, and Writing - original draft, S.S and M.L;

Investigation, Methodology, Project administration, Supervision, and Writing - review and editing, S.M and G.A. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY

No datasets were generated or analyzed during the current study.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

CONSENT FOR PUBLICATION

Not applicable

Highlights

- Early-stage maxillary sinus SCC shows good outcomes with surgical intervention
- Advanced-stage tumors frequently spread to nearby tissues
- Well-differentiated tumors lead to better prognosis
- Surgery combined with radiotherapy and immunotherapy offers improved treatment options.

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