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Management of the neck in maxillary sinus carcinomas

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Abstract

Purpose of Review—To discuss and review the role for elective treatment of the neck in maxillary squamous cell carcinoma. Improvements in survival have been seen due to improved local therapies and control, therefore the treatment of the neck has become a topic of debate.

Recent findings—The risk of occult metastases in neck nodes is higher for T 3-4 tumors. The rate of nodal relapse in the N0 neck without elective treatment is 8-15%. With elective irradiation the nodal relapse rate decreases. However, most nodal relapses are accompanied by local failure or distant disease. Local failure remains the most common site of failure and cause of death in this patient population.

Summary—Treatment failure occurs overall in 62% of all patients, with local recurrence by far the most common site of treatment failure which is rarely amenable to salvage therapy. Therefore elective neck irradiation is not routinely indicated in the clinically N0 neck; those who recur only in the neck can be surgically salvaged more than 50% of the time.

Keywords

maxillary carcinoma; elective neck therapy

Introduction

Primary malignant tumors of the sinonasal tract are rare. They account for less than 10% of head and neck cancers with an annual incidence of 0.5-1.0 per 100,000 people in the United States[1]. The maxillary sinus is the second most common sub-site, preceded only by the nasal cavity for neoplasia of epithelial origin arising in this area. Squamous cell carcinoma (SCC) is by far the most prevalent malignant histology, accounting for 57-80% of all malignant tumors. This is followed by minor salivary gland tumors, sarcoma, esthesioneuroblastoma, lymphoma, sino nasal undifferentiated carcinoma (SNUC) and melanoma which occur in decreasing frequency. As in the remainder of the head and neck region, smoking predisposes one to squamous cell carcinoma. SCC can also arise from inverting papillomas in 10% of cases and rarely in the background of chronic sinusitis. More unique risk factors however are

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exposure to wood dust, chemicals such as chromium, nickel and formaldehyde, which are associated with other malignant tumors, such as adenocarcinoms and clear cell carcinoma[2].

Presentation

Neoplasms of maxillary sinus or antrum of Highmore rarely present with symptoms at an early stage (Figure 1) as many lesions are asymptomatic until they become quite large[1]. Symptoms of obstruction or local invasion of adjacent tissue (soft tissue mass, loose teeth, anesthesia of V2, diplopia, proptosis, and trismus,) are often the first presenting sign. As such, 82% of patients present with advanced stage of disease (T3 or higher) (Table 1)[1]. However, even with advanced T stage, it is thought that the incidence of nodal metastasis is low, as the maxillary sinus does not have an extensive lymphatic drainage network[3].

In the 1930s Öhngren described an imaginary plane defined by a line joining the medial canthus of the eye to the angle of the mandible. This plane divides the region of the nasal cavity and maxillary sinus into half: the infrastructure (Antero inferior) and suprastructure (Postero superior) (Figure 2). This line was to delineate the easily resectable tumors of the infrastructure, from the more difficult, and harder to cure tumors of the suprastructure. Tumors of the infrastructure of the maxillary antrum may extend through the floor of the antrum into the oral cavity, through the medial wall into the nasal cavity and through the anterior wall to the soft tissues of the cheek or through the lateral wall into the masticator space. Lesions involving the suprastructure spread by extension through the posterior wall into the pterygomaxillary space, pterygopalatine fossa, infratemporal fossa and the middle cranial fossa; through the roof of the sinus into the orbit; or via the ethmoid cavities to the anterior cranial fossa (Figure 3). Tumors may also track along the infraorbital nerve to the gasserian ganglion[4]. Tumors of the infrastructure, generally produce symptoms early, and thus present at an earlier stage, and are more readily amenable to a satisfactory resection with an excellent chance for local control than lesions of the suprastructure.

Lymphatic Drainage of the Maxillary Sinus

The maxillary sinus is thought to be an area with paucity of lymphatic pathways with two main routes of lymphatic drainage: the ipsilateral jugulodigastric nodes and the retropharyngeal nodes. One drainage pathway runs from the maxillary gingiva to the submandibular nodes (level 1) through the buccal lymphatic vessels or buccinator nodes. The second pathway runs from the nasal floor to the upper jugular nodes through the retropharyngeal or parapharyngeal nodes[5,6]. Therefore the majority of observed nodal involvement occurs in level 1 and 2[3,7]. A review of T4 maxillary sinus SCC patients by Homma et al[8] (n=128) demonstrated that of those with cervical metastases at time of diagnosis, 96% had ipsilateral level 1b or 2 disease. However the retropharyngeal lymph nodes, level 3, level 4, and even contralateral neck can also be involved in a minority of patients, particularly those with advanced stage primary tumors, and those tumors which cross the midline (Figure 4). Yagi et al[9], when looking at all stages and histology of tumors arising in the maxillary sinus, also noted that cervical metastatic disease was most commonly found in the ipsilateral upper jugular region, followed by the submandibular region and then the lower jugular region. Less frequently bilateral disease was seen. Also

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retropharyngeal node involvement has been reported in 7-16%[6,8,10] of patients at time of diagnosis, as well in those developing regional failures[11].

Elective Management of the Neck in Maxillary Cancer

Due to the limited lymphatic drainage and rarity of regional disease at presentation, a topic of continued debate remains in regards to how best treat the N0 neck. Many papers have been published on this topic, including more recent reviews and a meta-analysis, underscoring the continued uncertainty and debate[2,5,7,8,12-19]. Current 2013 National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant radiation therapy to the N0 neck in the setting of T3 and T4a disease. However, for smaller primary lesions, (T1 and T2) no elective treatment of the neck is recommended. Most data on this topic consist of small series, with multiple histologies, multiple subsites, treated over a broad span of time with changing treatment patterns making interpretation difficult. It is accepted that different histologies have different propensities for nodal spread (Table 2) and as such, the risk of metastases changes based on tumor histology. Nodal metastases have been reported in as high as 28% of patients with squamous cell carcinoma, 25% for adenocarcinoma, 12% for undifferentiated carcinoma, and 10% for adenoid cystic carcinoma[20]. Another review has the incidence of lymph node involvement in nonsquamous cell carcinoma of the maxillary sinus at presentation even lower (in the range of 3-6%)[21,22].

In this review we are focusing on squamous cell carcinoma as it is the most common histology and appears to be the most aggressive in regards to nodal metastasis. In the literature the rate of involvement of regional lymph nodes, for SCC varies widely. Le et al[3] reports an overall incidence of lymph node involvement at diagnosis of 15.5% when only SCC pathology is taken into account. This is consistent with many reports[5,7,9,12,13,23-25] and due to this low number most authors have advocated no elective neck treatment for patients with maxillary sinus carcinoma. However, in the 1990s Paulino et al[7] and Jiang et al[21] began to advocate elective ipsilateral neck irradiation in all patients with SCC due to high incidence of neck relapse associated with SCC histology (28% to 36% in their respective reviews) and the poor prognosis of those who relapsed in the neck[7,21,26]. A review of the literature however, shows regional failure in the N0 neck to be significantly lower at 4%[24]-17%[14]; especially when looking at patients who did not have synchronous local failure[9,27](Table 3).

In an attempt to address the rate of nodal failure, one paper in the literature focused on the use of elective neck dissection in the management of SCC of the maxillary sinus. In Brown[15] et al's series, 13 patients with N0 necks underwent elective neck dissection. Even after neck dissection they had two neck recurrences in the ipsilateral dissected neck. This 15% (2/13) is consistent with their and our review of the literature of isolated neck recurrences in the non-treated neck (12%, range 5-36%)[15]. This is the only paper describing elective neck dissection in this patient population. One reason for this is that surgical clearance of the retropharyngeal nodal basin, that likely is at risk of occult nodal disease, is not possible. Therefore most other studies and the NCCN guidelines focus on elective irradiation to the neck in advanced tumors as irradiation to the ipsilateral upper jugular

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lymph nodes is not thought to bring about much additional morbidity and is well tolerated by the patient.

It is suggested that lesions which invade the hard palate, and present in the oral cavity, have a higher rate of nodal failure. This is due to the rich lymphatic pathways of the palate, and therefore they act more as an oral cavity primary rather than maxillary sinus tumor[5,8,13,15,28,29]. In Cantu's[12] series of 156 patients with SCC of the maxillary sinus, 16 patients (10%) had regional recurrence; 11 of which (68.7%) were T2 N0 at presentation. In addition, T4 lesions with extension to the hard palate have been reported to have a significantly decreased local control rate, as compared to all T4 maxillary sinus tumors[30,31]. A recent review of maxillary SCC originating in the oral cavity noted 38%[16] of patients with cervical metastases at diagnosis, of which 33% (17/52) had N2c disease. These lesions originated in the hard palate, and thus were not truly maxillary sinus cancers, and support the existing theory that there is increased drainage and lymphatic spread from the oral cavity as compared to the maxillary sinus[16].

While the true rate of nodal metastases at presentation and subsequent nodal failure in the untreated neck has been the recent topic of discussion, it is noted in these studies that local recurrence is still the most common cause of treatment failure, with a very morbid course, and low salvage rates. Giri et al[26] in 1991 noted that 49% (18 of 37) of their patients had a treatment failure with local recurrence as the most common site of failure in 16 out of the 18 cases. In contrast only three patients (8%) who were originally N0 and received no elective treatment of the neck developed cervical metastases. Two of the three of these recurrences also had recurrence at the primary site. Due to the frequency of local failure, routine neck irradiation was not recommended as the added morbidity of radiation did not overweight the small risk of having isolated neck failure. Kim et al[13] also reported a local failure rate of 68.1% as compared to a regional failure rate of 19% during follow-up (median, 6 years) of their patients.

Our review of the literature (Table 4) and MSKCC data (Figure 5) shows an overall recurrence rate of 44-68%. Local recurrence in each study was most common, accounting for 43-75% of all recurrences. Nodal failure was less often, occurring in 8-33% of all failures. Isolated nodal failure was observed in 4.8%[24] – 7.3%[17] of all patients when the primary site was controlled. Isolated neck failure accounted for 38-82% of all the cervical failures. The rate of isolated neck failure is similar to the rate of patients with distant failures[24]. In the largest series published, Cantu et al, reported 31 isolated neck failures out of 230 recurrences in 399 maxillary sinus cancer. Of these 30 (97%) were able to be surgically salvaged[12] and only 2 died as a result of isolated neck metastasis[12]. Similarly Dirix[33] and Porceddu[34] reported the salvageability of isolated neck failures. These isolated failures occurred in the ipsilateral level 1b and 2 and as such allowed for identification and appropriate intervention. The occurrence of retropharyngeal nodes and overall medical status were the limiting factors keeping isolated nodal recurrences from being surgically salvaged. While neck disease is able to be salvaged > 50% of the time, recurrent local disease is extremely morbid and only 8[9,32] - 20%[9] of isolated local failures are salvaged. Local failure is the most common cause of death in these patients[32].

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Le[3] and Guan[11] had patients, originally N0, who underwent elective neck irradiation (ENI) to the retropharyngeal and cervical nodes. Though both were small series (n= 25 and 11 respectively) none of the patients who received ENI developed nodal metastasis. However 10%[3] and 18%[11] of those who did not receive ENI suffered neck failures. Therefore they support the use of elective irradiation to the ipsilateral level 1b and 2a during primary treatment, as there are few critical adjacent structures so late complications related to ENI of these echelons would be rare. Jiang[21] looked at the survival for those who underwent ENI vs those who recurred in the neck that were able to be salvaged. The 10y disease specific survival (DSS) was 34% in those with no ENI and 58% in those who received ENI. Based on this MD Anderson changed their treatment practice to irradiate the neck in T2-4 SCC or undifferentiated maxillary sinus carcinoma.

Survival

Over the past decades, better imaging assessments of the primary tumor have allowed adequate surgery and adjuvant therapies leading to improved local control[24,25,35]. Thus attention is now focused to metastatic disease and survival. In Takes[18] et al's review, median survival of patients who remained N0 was 80 months while those with any cervical involvement was 25 months (p=0.05). This is similar to Wu's[36] and Kim's[12] reviews that noted how node involvement at presentation affected survival. The 5 year survival rate with negative nodes was 31.3%[12] - 55%[36] while for those with positive nodes it was 16.7%[12] – 17%[36] (p=0.03). Lee et al[3] also reported that patients with nodal relapse had a significantly higher risk of distant metastasis based on univariate (p=0.02) and multivariate analysis (HR=4.5, p=0.006)[2]; with the 5year actuarial risk of distant relapse being 29% for patients with neck control as compared to 81% for patients with neck failure[3]. However, the most powerful prognostic factor for overall survival remained T stage[25,29](p=0.026[35]) followed by nodal involvement (p=0.036[35]). Therefore, while the presence of nodal relapse has been associated with decreased survival it is rarely the cause of death. The presence of nodal disease is a sign of an aggressive and advanced phenotype; one associated not only with neck disease but local failure and distant metastatic disease. A meta-analysis, published this year, found that elective neck irradiation can significantly reduce the rate of nodal recurrences[19] however it is unclear whether this improved regional control impacted on survival.

Conclusion

A majority of patients with malignant tumors of the maxillary sinus present at an advanced T stage which directly affects survival (Figure 6 and 7). Treatment failure occurs in 62% of all patients, with local recurrence by far the most common site of treatment failure which is rarely amenable to salvage therapy[24,37-39]. Regional failure is less common and occurs in only 3-20% of all treated patients. Most cervical relapse is accompanied with uncontrollable primary or distant relapse, explaining the poor survival of those with cervical relapse. Patients with cervical relapse alone can be salvaged in 50-70% of cases[29]. Local failure is the primary cause of failure in any stage[29] and as such, aggressive therapy to achieve maximum local control of the primary tumor is considered to be more important than elective neck treatment[13]. Thus, based on our own experience, elective treatment of the neck

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can only be considered justifiable in patients with advanced stage primary carcinomas (T3-4) of the maxillary sinus. If the neck on the ipsilateral side is entered for example, to accomplish vascular anastomosis of a free flap, then elective neck dissection is performed at that time. If the neck is not entered, then elective irradiation of the neck, in conjunction with postoperative RT to the primary site, is recommended for T 3-4 tumors. Elective treatment of the neck in early stage tumors (T 1-2), is not recommended.

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Key Points

1. Treatment failure occurs in 62% of all patients, with local recurrence by far the most common site of treatment failure in any stage; local failure is rarely amenable to salvage therapy
2. Most cervical relapse is accompanied with uncontrollable primary or distant relapse, explaining the poor survival of those with cervical relapse.
3. Patients with cervical relapse alone can be salvaged in 50-70% of cases.
4. Aggressive therapy to achieve maximum local control of the primary tumor is considered to be more important than elective neck treatment.
5. Elective treatment of the neck can only be considered justifiable in patients with advanced stage primary carcinomas (T3-4) of the maxillary sinus.

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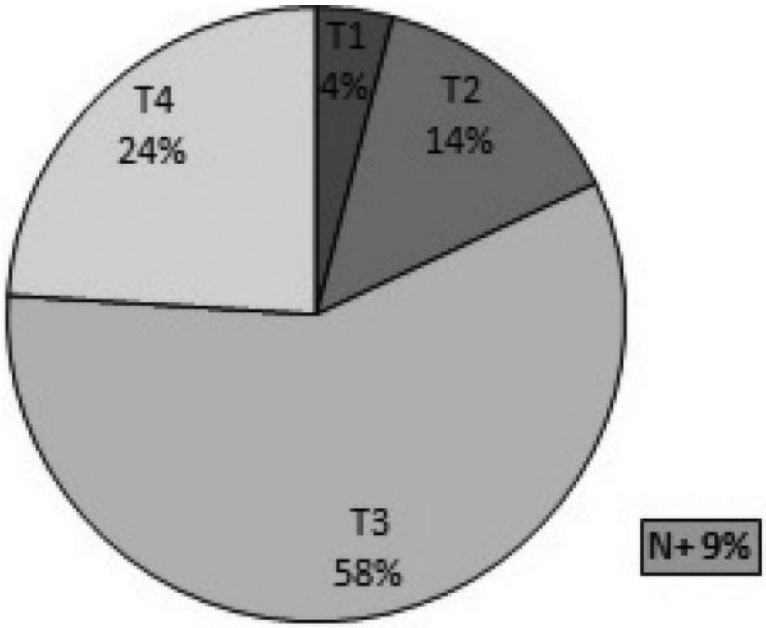

Figure 1.
Distribution of the T categories of squamous cell carcinoma of the maxilla at the time of diagnosis[1] (Data from MSKCC)

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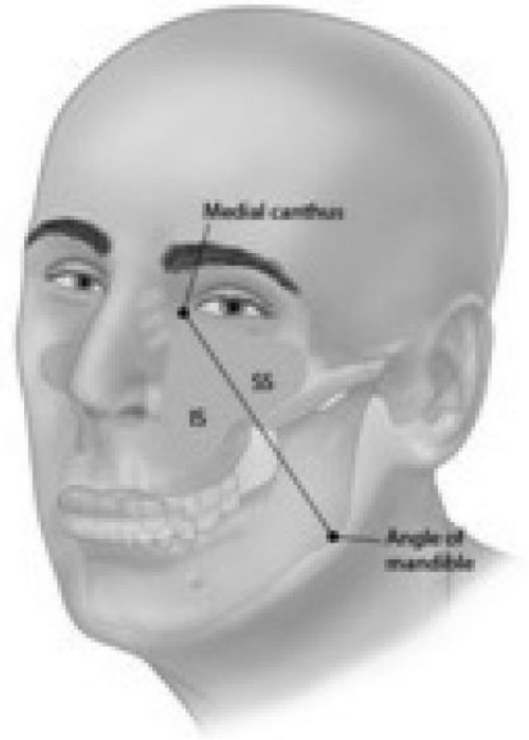

Figure 2.
Öhngren's line - The anatomic region located anterior and inferior to this plane is called the infrastrucre and the region posterosuperior to this plane is called the suprastructure.[1]

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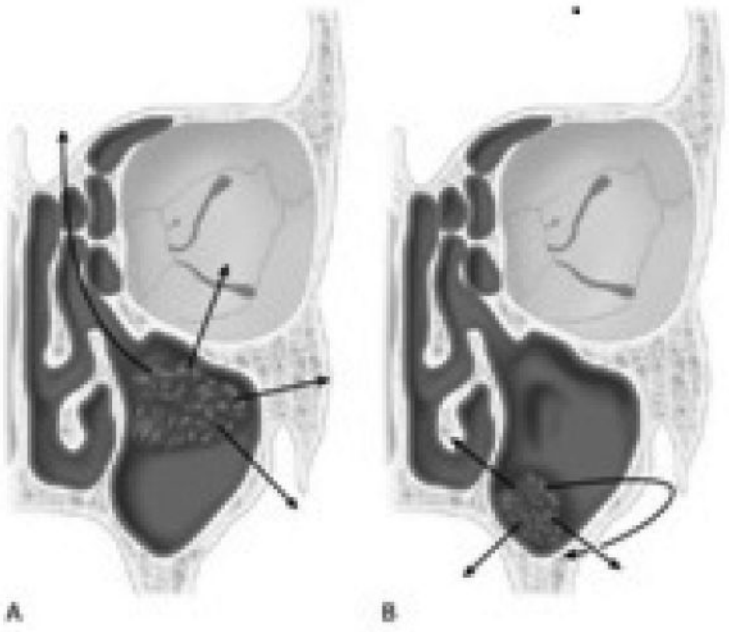

Figure 3.
Routes of spread of tumors of the maxillary antrum. A- Suprastructure. B-Infrastructure[1]

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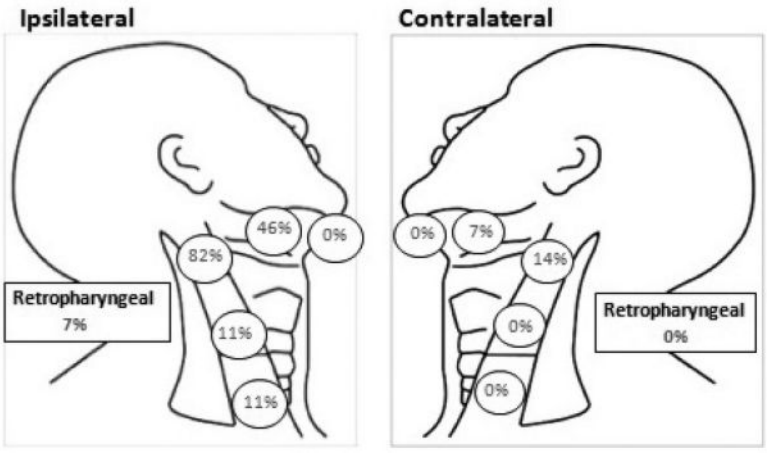

Figure 4.
Lymph node metastases distribution at presentation for T4 maxillary sinus squamous cell carcinoma.

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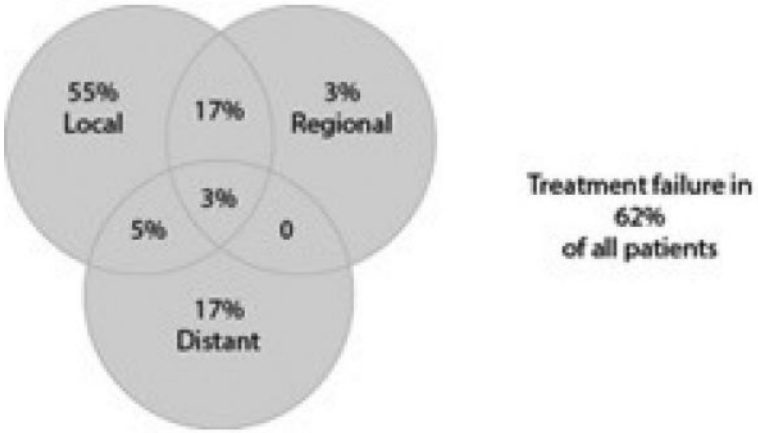

Figure 5.
MSKCC data on site of failure of maxillary sinus SCC.[1]

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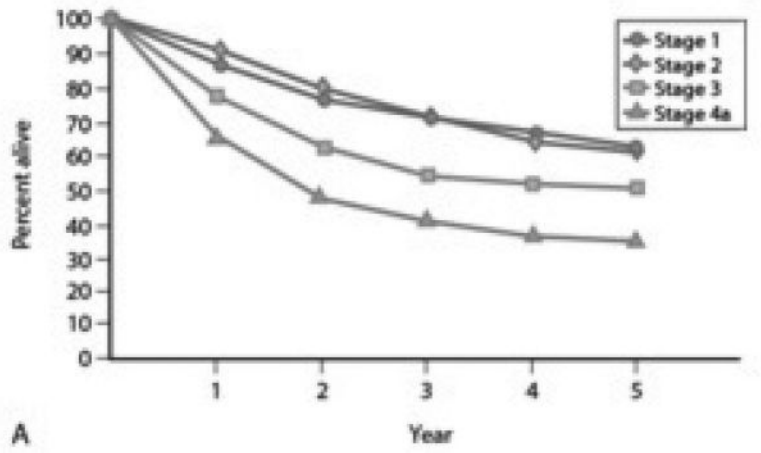

Figure 6.
Overall 5y survival of nasal and paranasal disease with all histology by stage[1]

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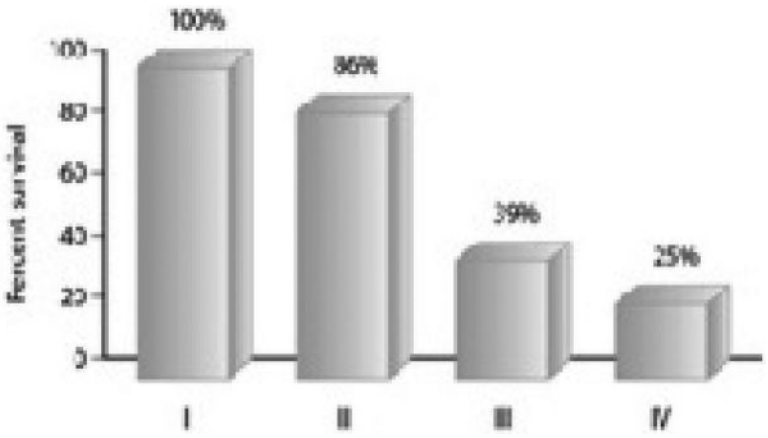

Figure 7.
Overall 5y survival of maxillary sinus SCC by stage[1]

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Table 1

Tumor staging of maxillary sinus carcinoma[1]

Tstage	Description
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, or ethmoid sinuses
T4a	Moderately advanced local disease. Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, or sphenoid or frontal sinuses
T4b	Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus

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Table 2

Survival of maxillary sinus carcinoma based on histology. Adapted from Bhattacharyya[25]

Tumor Type	n	Percentage	Mean Survival (months)	Median Survival (months)	5year survival (percentage)
Adenocarcinoma	31	4.8	69	50	47.7
Adenoid Cystic Carcinoma	64	9.8	79	118	57.5
Mucoepidermoid Carcinoma	15	2.3	58	53	35.9
Other	70	10.8	53	27	38.7
Sarcoma	46	7.1	63	47	44.8
Squamous Cell Carcinoma	401	61.7	44	18	29.2
Melanoma	23	3.5	30	18	25.9
Overall	601	100	52	25	35

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Table 3

Incidence of nodal disease at presentation and after treatment[2,3,5,7-9,12,13,14,21,24-27].

Study	Overall % with nodes at presentation	SCC% with nodes at presentation	Treatment of N0 neck	Overall N0 patients with nodal failure	SCC N0 patients with nodal failure
Hinerman 2011[2]*!*	--	--	None	--	2/22 (9%)
	--	--	ENI unilat ENI bilat	--	1/14 (4%)*#* 0/9
Le 2000[3]*@*	11/97 (11.3%)	9/58 (15.5%)	None	10/97 (10.3%)	20%
	--	--	ENI	0/25 (0%)	--
Valentino 2010[5]*@*	2/17 (11.7%)	1/7 (14.3%)	none	--	--
Paulino 1997[7]*!*	--	4/42 (9.5%)	None	--	11/38 (28.9%)
Homma 2014[8]*#*	--	28/128 (21.9%)	none	--	8/83 (9.6%)
Yagi 2001[9]*@*	9/118 (7.9%)	--	None	9/109 (8.3%)	--
Cantu 2008[12]*@*	33/399 (8.3%)	16/156 (10.3%)	None	51/399 (12.5)	--
Kim 1999[13]*!*	--	12/116 (10.3%)	None	14/104 (13.5%)	14/104 (13.5%)
Mirghani 2013[14]*$*	8/155 (5.2%)		None	16/133 (12.0%)	
Jaing 1991[21]*@*	6/73 (8.2%)	--	none	11/50	--
	--	--	ENI	0/17	--
Dulguerov 2001[24]*@*	3/103 (2.9%)	--	none	(4%)	--
SEER 1988-1998[25]*@*	45/601 (7.5%)	--	--	--	--
Giri 1991[26]*@*	3/41 (7.5%)	--	--	3/35 (8%)	
Syners 2009[27]*$*	18/168 (11%)	10/55 (18%)		11%	11%

ENI, elective neck irradiation

! SCC of maxillary sinus

@ includes all malignant histologies originating in the maxillary sinus

T4 SCC lesions of maxillary sinus

$ includes all histologies and subsites in paranasal sinuses

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Table 4

Recurrence patterns after primary treatment[3,5,7,9,11,13-15,21,24,26,27,32].

Study	Overall Recurrence	Local Recurrence	Isolated Local Failure	Nodal Recurrence	Isolated Regional Failure	Distant Disease	Isolated Distant Failure
Le 2000[3]@	65/97(67%)	46/97 (47%)	45/46 (98%)	8/97 (8%)	7/8 (86%)	12/97 (12%)	--
Valentino 2010[5]@	1/7(14%)	1/7 (14%)	1/1 (100%)	0	--	0	--
Paulino 1997[7]!	28/42 (67%)	19/42 (45%)	13/19 (68%)	14/42 (33%)	7/14 (50%)	5/42 (12%)	0/5 (0%)
Yagi 2001[9]@	--	35/106 (33%)	--	9/ 106 (8.3%)	7/9 (78%)	--	--
Guan[11]#	26/59 (44%)	18/26 (69%)	12/18 (67%)	7/26 (27%)	3/7 (43%)	7/26 (27%)	3/9 (33%)
Kim 1999[13]!	79/116 (68%)	79/116 (68%)	57/79 (72%)	22/116 (19%)	0/22 (0%)	--	--
Mirghani 2013[14]$	68/133 (51%)	51/68 (75%)	40/51 (78%)	16/68 (24%)	6/16 (38%)	16/68 (24%)	9/16 (56%)
Brown[15]!	--	9/18 (50%)	--	2/18 (11%)	0/2 (0%)	--	--
Jaing 1991[21]@	33/73 (45%)	14/73 (19%)	10/14 (71%)	11/73 (15%)	9/11 (82%)	12/73 (16%)	8/12 (67%)
Dulguerov 2001[24]@	114/220 (52%)	86/103	73/86 (85%)	14/103 (14%)	8/14 (57%)	18/103 (17%)	9/18 (50%)
Giri 1991[26]@	18/37 (49%)	16/37 (43%)	NR	5/37 (14%)	2/5 (40%)	1/18 (6%)	--
Syners 2009[27]$							
Kreeft 2011[32]!	--	20/69 (29%)	--	16/69 (23%)	--	2/69 (3%)	--

! SCC of maxillary sinus

@ All histologies present in maxillary sinus carcinoma

SCC of paranasal sinuses

$ Includes all histologies and subsites in paranasal sinuses