REVIEW ARTICLE

The controversy in the management of the N0 neck for squamous cell carcinoma of the maxillary sinus

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Abstract Squamous cell carcinoma (SCC) of the maxillary sinus is a relatively rare disease. As the reported incidence of regional metastasis varies widely, controversy exists as to whether or not the N0 classified neck should be treated electively. In this review, the data from published series are analyzed to decide on a recommendation of elective treatment of the neck in maxillary SCC. The published series consist of heterogeneous populations of different subsites of the paranasal sinuses, different histological types, different staging and treatment modalities used and different ways of reporting the results. These factors do not allow for recommendations based on high levels of evidence. Given this fact, the relatively high incidence rate of regional metastasis at presentation or in follow-up in the untreated N0 neck, and the relatively low toxicity of elective neck irradiation, such irradiation in SCC of the maxillary sinus should be considered.

Keywords Maxillary sinus · Squamous cell carcinoma · Head and neck cancer · Elective neck treatment

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Introduction

Malignant tumors of the paranasal sinuses are relatively rare and represent approximately 3 % of the malignancies of the head and neck, of which 80 % arise in the maxillary sinus. Squamous cell carcinoma (SCC) is the most common malignant tumor at this site, representing 60–90 % of the cases [1–3]. Because these tumors often progress without obvious clinical symptoms, most of the patients present with disease that is already very advanced.

In general, the presence of neck metastasis is considered to be one of the most important prognostic factors in head and neck SCC. The incidence of neck metastasis in SCC of the maxillary sinus has not been well defined, but has traditionally been believed to be low. This belief is based on the assumption that the chance for nodal metastasis is low in tumors arising in sites without an extensive lymphatic network. However, the published incidence of regional metastasis in patients with maxillary sinus SCC are varied and range widely. Thus, recommendations for the management of the clinically negative neck (N0) in these patients conflict among various authorities.

The aim of the present article is to review the literature regarding the incidence of lymph node metastases and the management of the N0 neck in patients with maxillary sinus SCC.

Incidence of lymph node metastasis

The incidence of lymph node metastasis in maxillary sinus SCC at presentation and in follow-up has been studied and reviewed by several authors [1–23].

Paulino et al. [5] in 1997 analyzed 42 consecutive patients with SCC of the maxillary sinus, treated from 1971 to 1995. One tumor was classified as T1, 5 T2, 15 T3, and 21 T4. Four of 42 patients (9.5 %) had clinically apparent cervical lymphadenopathy at initial presentation. Thirty-three patients had surgical resection and radiotherapy and 9 had radiotherapy alone. None of the 38 patients with clinical N0 neck received elective treatment to the cervical lymph nodes. Of these 38 patients, 11 (28.9 %) subsequently developed clinically obvious lymph node metastases that were isolated to ipsilateral lymph nodes in 9 cases, contralateral nodes in 1 case, and bilateral nodes in another 1. However, 5 of these 11 patients with neck recurrences also had local failure. The most common sites of neck metastases were the nodes in the sublevel IB and level II. Only tumor stage was found to be significantly associated with the risk of neck relapse, with T1 and T2 tumors having a higher percentage of relapse than T3 and T4; however, as only five patients had T1 or T2 tumors, a statistically valid comparison of risk could not be made.

Moreover, this observation may be explained by the fact that all patients received radiotherapy and although no elective treatment was given to the neck, the lymph nodes closest to the primary tumor site may have been included in the radiation fields, particularly for the larger tumors. Other factors such as tumor subsite within the maxillary sinus, involvement of the oral cavity/oropharynx, nasal cavity, nasopharynx or orbit were not predictive of cervical node relapse in this study. The median overall survival for patients who remained N0 was 80 months, whereas for those with initial cervical involvement or recurrence in the neck it was 25 months ($p = 0.05$). Based on this figure and the rate of metastases in the N0 neck of 28.9 %, the authors recommended ipsilateral elective neck irradiation (ENI) in patients with T1–T4 SCC of the maxillary sinus.

Le et al. [2] in 2000 reviewed the records of 97 patients with maxillary sinus carcinoma treated with radiotherapy between 1959 and 1996. Of these, 58 patients had SCC, 4 adenocarcinoma, 16 undifferentiated carcinoma, and 19 adenoid cystic carcinoma. Eight of the 97 patients had T2, 36 T3, and 53 T4 tumors. Eleven patients had nodal involvement at diagnosis including 9 of the 58 with SCC (15.5 %). The most common sites of nodal involvement were the ipsilateral levels I and II. Thirty-six patients were treated with definitive radiotherapy alone, and 61 received a combination of surgery and radiation. Thirty-six patients had neck irradiation; the neck was staged N0 in 25 of these. Within this subset, the histologic type of the carcinoma was not disclosed. The 5-year risk of neck relapse was 14 % for SCC. The overall risk of nodal involvement at either initial diagnosis or at follow-up was 28 % for SCC. All patients with nodal involvement had T3–4 tumors and none had T2 tumors. ENI effectively prevented nodal relapse in patients with SCC and N0 neck: the 5-year actuarial risk of nodal relapse was 20 % for patients without ENI and 0 % for those with elective neck treatment. There was no correlation between neck relapse and primary tumor control. The most common sites of nodal relapse were in the ipsilateral levels I–II of the neck (11/13). Patients with nodal relapse had a significantly higher risk of distant metastasis based on univariate ($p = 0.02$) and multivariate analysis (hazard ratio = 4.5, $p = 0.006$). The 5-year actuarial risk of distant relapse was 29 % for patients with the neck controlled versus 81 % for patients with neck failures. There was also a trend for decreased survival with nodal relapse. The 5-year actuarial survival was 37 % for patients with neck control and 0 % for patients with neck relapse. Based on these findings, ENI in patients with T3–4 SCC of the maxillary sinus was recommended.

Cantù et al. [6] in 2008 reported 704 cases of paranasal sinus malignancies treated between 1968 and 2003, both untreated tumors (60 %) and recurrences (40 %). All

patients were treated with surgery alone or combined with chemotherapy and/or radiotherapy, without elective neck dissections. There were 399 maxillary sinus tumors (156 SCC, 26 undifferentiated carcinomas, 91 adenoid cystic carcinomas, 27 mucoepidermoid carcinomas, 18 adeno-carcinomas, 59 sarcomas and rare forms). Considering the maxillary sinus cases, the highest cumulative incidence for nodal metastases at 5 years was for T2 tumors of all histological tumor types (18 %) and for SCCs (20.7 %). Among the 77 patients with SCC stage T2, the incidence was 26 %. All patients who developed nodal metastasis underwent neck dissection with or without postoperative radiotherapy as treatment for their nodal metastasis, unless the nodal disease was unresectable. However, 54 % of the patients with recurrent tumors who were also included in the analysis received radiotherapy as part of their treatment and it is unclear which patients received (elective) neck irradiation.

From the data described above, the authors concluded that the rate of nodal metastases from a malignant maxillary sinus tumor was quite low at presentation; 8.3 % for all histological types and 16/156 (10.3 %) for SCC, of which 11/16 occurred in T2 tumors. A hypothesis that could explain why tumors staged as T2 had a higher rate of regional metastasis at presentation than T3 and T4 tumors was that "T2" is defined as a tumor involving the floor of the maxillary sinus with possible invasion of the mucosa of the hard palate and upper gum, and/or the inferior nasal cavity. These structures have a lymphatic network that is denser than that of the mucosa of the paranasal sinuses. Therefore, with regard to lymph node metastases, such tumors may exhibit behavior similar to that of oral cancers rather than paranasal sinus cancers. Furthermore, the authors concluded that while early or late lymph node metastasis was an unfavorable prognostic factor, only rarely did it represent the cause of death. This paradox is explained by the correlation of regional with distant disease [12] and mortality [8]. The authors stated that elective neck treatment was not indicated in patients with T3 and T4N0 tumors, while elective treatment of the neck might be considered for T2N0 SCC. However, the series only partially consisted of previously untreated tumors, so one must be aware of possible bias.

In a series of 118 patients with maxillary sinus carcinoma, Yagi et al. [7] found that the incidence of cervical lymph node metastasis at the initial diagnosis was 7.9 % (n = 9), and that the rate of secondary cervical lymph node metastasis without recurrence at the primary site after the first treatment was 8.3 % (n = 9). Among the nine patients with cervical lymph node metastasis detected at the first examination, three developed distant metastasis as did three of the nine with secondary cervical metastasis. Similar rates were observed by Kim et al. [8] among 116

patients with maxillary SCC. Twelve patients (10.3 %) presented initially with neck node metastases and 14 (13.5 %) of 104 node-negative patients subsequently developed regional recurrence. During the follow-up period, regional failure was far less common than local failure (19.0 vs. 68.1 %), and the majority of regional failures were accompanied by local recurrence. Oral cavity extension and control status of local disease were the high-risk factors for subsequent development of regional recurrence in node-negative patients. The overall 5-year survival rate for node-positive patients (16.7 %) showed a worse outcome than for node-negative patients (31.3 %).

In a recently published retrospective series of Mirghani et al. [9] involving 155 consecutive patients treated for malignancies of the maxillary sinus, ethmoid and nasal cavity between 1995 and 2005, 25 patients had SCC of the maxillary sinus. Of the 44 maxillary tumors of different histology, all but one were T3 or T4. No elective neck treatment was administered. Given the heterogeneity of this series, the data on occult metastasis in maxillary SCC in particular cannot be identified. The 5-year nodal failure rate in the 47 SCCs of all sites was 17.6 %.

In another recently published retrospective analysis of 168 patients treated for sinonasal cancer between 1986 and 2006, Snyers et al. [23] also found a relatively high percentage of regional failure for SCC of the maxillary sinus as compared to other subsites and histological types. Cervical lymph node metastases at presentation were found in 18 patients (11 % of the entire population), including 10 of 55 patients (18 %) with SCC. Excluding three patients who underwent ENI, for all subsites nodal recurrence rates in the untreated N0 neck were 11, 12, and 33 % for SCC, adenocarcinoma, and melanoma, respectively. A relatively high regional recurrence rate of 21 % was observed in a subgroup of 19 patients with T3–T4 SCC of the maxillary sinus. The authors considered this a recommendation for ENI for these patients.

Choice of management of the N0 neck

A relatively high rate of failure in the clinically N0 neck has been reported in several retrospective series. When the neck is not treated electively, the reported rates of failure range from 9 to 33 % [2, 5, 10, 16].

A few recent papers specifically addressed the issue of elective treatment of the N0 neck in maxillary SCC. The most recent report consisted of a limited series of 18 patients with maxillary sinus SCC who were treated surgically. One patient had metastasis at presentation. Of the 17 patients with a clinically uninvolved neck, 13 underwent an elective neck dissection (because the neck needed to be entered for free flap reconstruction). Among 13 patients

who had an elective selective neck dissection, the neck was involved in one case (1/13: 8 %). Four patients had regional metastases, two with positive nodal disease confirmed after elective and therapeutic neck dissection, respectively, and two who developed regional recurrence, both after elective selective neck dissections which were negative (pN0) [17]. Reviewing the literature, they identified no other report on elective neck dissection for this particular tumor site. In a literature review, the authors found a mean regional recurrence rate of 12 % and a total mean regional metastatic rate of 21 % (including metastases at presentation). Local recurrence was identified as the main issue in disease control. Nine of 18 patients developed a local recurrence despite 15 of them having received postoperative radiotherapy. Salvage surgery was not feasible in any of the patients with local recurrence. The authors concluded that elective selective neck dissection did not contribute to an improved rate of neck control with regional recurrence of 11 % (2/18) in their electively dissected patients compared with a 12 % rate of regional recurrence alone (so, without local recurrence) in initially cN0 classified cases in the review. There is no evidence in this report to indicate that elective selective neck dissections for maxillary sinus SCC will result in better disease control.

In the previously discussed series reported by Le et al. [2], none of the patients with maxillary sinus SCC who were staged cN0 at presentation and who received ENI relapsed in the neck, whereas 20 % of patients who did not receive ENI had regional relapse. They found a significant association between neck control and the risk of distant relapse. The question remains whether this is merely an association reflecting aggressive intrinsic tumor behavior leading to both regional and distant relapse, or a causal relationship between neck control and the development of nodal metastasis. In the latter it would support the use of elective neck treatment, whereas in the former elective treatment would not prevent distant metastasis and would not really influence survival.

Radiotherapy, with or without surgery, as a treatment modality for (regional treatment of) maxillary SCC is reported to be an effective alternative to surgery for elective treatment of the neck and an effective adjuvant treatment for the primary tumor. Hinerman et al. [16] in 2011 analyzed 54 patients with maxillary sinus SCC who were treated from 1969 to 2006. All patients underwent radiotherapy, with or without associated surgical resection. Fifty-two (96 %) patients had clinical stages III or IV tumors, and 45 (83 %) had the neck staged as cN0, so 17 % had metastasis at presentation. ENI for the N0 neck was administered at the treating physician's discretion. Of the 45 patients with N0 necks, 23 received ENI, 14 unilaterally and 9 patients bilaterally. Of these 23 patients, 1 (4 %) who received unilateral irradiation failed in the contralateral neck. Of the 22 patients receiving no ENI, 2 (9 %) failed in the ipsilateral neck, one classified T2N0 and the other T3N0. Five-year local control (LC) rates by T stage were 63 % for T2/T3 and 43 % for T4 tumors. Five-year LC rates for patients treated with radiotherapy preoperatively, postoperatively, and definitively were 61, 65, and 37 %, respectively. Initially, overall 5-year rates for LC, neck control, and local regional control were 49, 82, and 45 %, respectively. The ultimate 5-year LC, neck control, and local regional control after salvage treatment of failures were 51, 87, and 50 %, respectively. The overall 5-year cause-specific survival was 41 %. The conclusion of this study was that radiotherapy, with or without surgical resection, remains an effective tool in treating patients with this disease.

An interesting observation was reported by Jang et al. [18] who analyzed treatment results of definitive radiotherapy in a group of 30 patients with maxillary sinus SCCs. All had clinically N0 disease and ENI was not used in any of the patients. Instead, 66 % received neoadjuvant chemotherapy and an additional 10 % had concomitant chemoradiation. Although the majority had advanced-stage disease (T4 in 73 % of cases), regional recurrence developed in only one patient, suggesting that either the incidence of regional metastasis was exceptionally low (also considering that all cases were N0 at presentation) or that systemic drugs might also have the capacity to eliminate occult micrometastases in regional lymphatics, comparable to ENI or surgery. Again, local failure was the main problem in this series.

An important point of discussion is the risk of metastasis in retropharyngeal lymph nodes (RPLNs). The presence of RPLN metastasis of primary head and neck cancer often receives less consideration than lymph node metastasis in the neck. With improvements in imaging techniques, there is an improved understanding of the risk and subsequently the need for treatment of RPLNs. The rates of RPLN metastasis from carcinomas of the nasopharynx, oropharynx, hypopharynx, postcricoid region, maxillary sinus, and cervical esophagus would be sufficiently high to warrant routine treatment, either electively or therapeutically, for this region. Through improved diagnostic techniques and heightened awareness of RPLN metastasis, patients at risk for having these metastases can be treated more effectively, mainly with radiotherapy [24]. However, in most published series on maxillary SCC, no relapses are reported in these nodes which may be explained by the fact that they may have been included in the radiation fields for the primary tumor in some series. In cases that did not receive elective neck treatment, this reasoning would not be applicable, challenging the relevance of RPLN in these tumors.

Discussion

From the published series, all of which are retrospective, the best evidence that one can retrieve remains hampered by several factors that should make one cautious in drawing firm conclusions. In these series, no elective neck dissections were performed, and therefore the actual histopathological status of the necks are not available; thus necessitating quantifying the rate of occult metastasis only by extrapolation based on the rate of regional recurrences. However, if the initial N0 neck received radiotherapy, this extrapolation is unreliable since this treatment may have eliminated occult metastatic deposits. Moreover, most authors do not clearly separate isolated neck recurrences from those associated with local recurrences, and therefore the separation between nodal relapses that could be attributed to occult metastasis at presentation and those attributable to local recurrences cannot be made. Many patients receive radiotherapy as part of their treatment and the inclusion of the neck in radiotherapy is variably reported. In the only study where the neck was electively treated surgically, selective neck dissection did not contribute to an improved rate of neck control, but this study included a limited number of only those cases that needed incision of the neck to perform free flap reconstruction. [17].

Moreover, given the limited number of patients, all T stages are clustered and the study populations differ in the distribution of T stages. Some series contained relatively low proportions (36–61 %) of patients with T3 or T4 disease [6, 20, 21], whereas others had up to 85–94 % T3 and T4 classified tumors [5, 8, 22, 23]. These differences may be explained by differences in the populations and also by the staging methods and criteria which may have differed in time and between centers. For example, in some series a significant part of the patients had been staged by plain X-ray films of the sinuses in the pre-CT and MRI era. This time factor may also have influence on outcome data, as radiotherapeutic techniques, including fields, have been improved considerably over time.

Some authors argue that since the prognosis in T3 and T4 tumors is significantly determined by local disease control and most maxillary sinus SCC are advanced stage, elective treatment of the neck is less relevant. Moreover, nodal spread may be a sign of aggressiveness of the primary tumor also expressed in a higher rate of distant metastasis and not the actual cause of distant disease.

On the other hand, there are many published series indicating that the rate of failure of the untreated N0 neck is relatively high and warrants elective treatment. Moreover, in those patients in whom the neck needs to be entered for free flap reconstruction, elective neck dissection will not impose much additional morbidity or effort. In the case of radiotherapy, much of the associated toxicity is secondary to the treatment of the primary tumor and not to the upper neck [2, 5, 10]. So, irrespective of the discussion of whether regional metastasis is a causal factor in distant metastasis or merely associated with it, elective neck treatment is effective in obtaining regional control and does not result in much additional toxicity.

Of course, a prospective randomized study could provide the best data on the effectiveness of elective neck dissection or ENI in maxillary sinus SCC. However, given the rarity of the disease such a trial would be difficult if not unfeasible to conduct. It would be helpful if future publications of retrospective data on maxillary sinus SCC would present these data in a more uniform and structured way, e.g., with results stratified according to T stage; the incidence of metastasis at presentation; how the nodal status at presentation was established (clinically, radiologically, cytologically); which, if any (elective) treatment was given to the neck; and the percentage of delayed metastasis (in the untreated N0 neck in particular).

Conclusions

Balancing the available retrospective data, heterogeneous as they are, we suggest that the regional lymphatics should be treated in these patients electively. The question is whether this should be considered only in the more common T3 and T4 classified tumors or for T2 lesions as well. For the latter category, it is more difficult to draw conclusions as they are infrequent and the reports in the literature are more contradictory. Further investigation is needed.

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