

## Role of Elective Neck Management in Maxillary Sinus Squamous Cell Carcinoma

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### Abstract

Maxillary sinus carcinoma is relatively rare. Standard treatment consists in surgery followed by adjuvant radiotherapy or chemoradiotherapy. The rate of neck lymph node metastasis during follow-up is about 5-30% and this event is a poor prognostic factor. It often occurs in large primary tumours (T3-T4). The role of prophylactic neck management, selective neck dissection (SND) or elective neck irradiation (ENI), remains unclear in N0 patients. Few studies specifically discuss the role of SND. A French study suggested SND could be proposed when primary surgery is feasible, especially for high tumour volume (T3-T4). Besides, it can be useful for lymph node staging and determining radiotherapy dose and volume. The role of ENI remains unclear and controversial, although some studies suggest a potential reduction of neck relapse with it. ENI (ipsilateral level II, +/- Ib and III or bilateral neck according to the primary tumour extension) could be proposed in selected patients, especially for T3-4 disease and when SND has not been performed. Intensity-modulated radiotherapy (IMRT) should be considered, whenever feasible, to reduce toxicity.

**Keywords:** Maxillary sinus; Squamous cell carcinoma; Neck irradiation

### Introduction

Paranasal sinus cancers make up less than 3% of head and neck malignancies, of which 80% are located in the maxillary sinus [1]. Squamous cell carcinoma (SCC) represents 60-90% of the histology. They are stage T3-T4 in around 65-70% and are associated with cervical lymph node involvement in around 5-10% [2].

The main issue of this disease is a high local relapse rate [3]. Standard treatment consists in surgery followed by adjuvant radiotherapy or chemoradiotherapy [4]. Positive surgical margins are a significant prognostic factor of local relapse, and adjuvant external-beam radiotherapy (EBRT) is required. When surgery isn't feasible due to high risk of resection morbidity in locally advanced stage (T3-T4) disease, concomitant chemoradiotherapy (CRT) is standard of care [5].

The rate of lymph node metastasis during follow-up is relatively low; it varies between 5% to 30% according to series, but represents a poor prognostic factor [6]. The distinction between isolated regional relapse due to occult nodal involvement causing metastasis, and regional metastatic relapse due to local relapse, remains unclear. Lymphatic drainage of nasal and paranasal cavities occurs in two directions, the anterior facial direction with most frequent sites being levels IIa, Ib and III, and the posterior direction towards retropharyngeal nodes [7,8]. However, the incidence of posterior node invasion is quite low [9]. Controversy remains in the management of the neck when no lymph nodes are involved at diagnosis (clinical N0 disease). The role of selective neck dissection (SND) and elective neck irradiation (ENI) remains unclear. The aim of this short review is to discuss neck management for patients without initial clinical neck node involvement.

Due to the low incidence of this disease, no randomized prospective studies are available on the subject. Table 1 contains the most important retrospective reports that have explored the regional outcome of patients with maxillary sinus cancers.

### Neck outcome when no neck management is performed

One of the oldest series by Jiang et al., from 1991, showed 11 neck relapses of 50 patients with N0 maxillary sinus cancer treated exclusively for primary tumour, without prophylactic neck treatment [10]. Of them, 9/11 (81.8%) had isolated neck recurrences. All of the 9 patients received salvage treatment (4/9 underwent definitive EBRT and 5/9 received combined management with EBRT and surgery).

Similarly, Paulino et al. reported 38 N0 diseases of 42 patients with maxillary sinus SCC [11]. None of them received prophylactic neck treatment. They found 11/38 (28.9%) neck metastases during follow-up. Most common sites were levels Ib and II. More recently, Kim et al. and Jang et al. only reported 14/104 (13.5%) and 1/30 (3.33%) neck relapses, respectively, in N0 maxillary sinus cancer patients without any prophylactic management [3,12].

Also, Sakashita et al. reported only 4/48 (8.3%) neck relapses after superelective intra-arterial chemoradiotherapy with Cisplatin, without prophylactic ENI, raising the question of balance between efficiency of elective neck radiotherapy alone and global effect of concomitant chemoradiotherapy [13]. Three out of four patients received salvage neck dissection. Mortality rate from regional disease was 1/48 (2%).

The above results are controversial in regard to the incidence (3.3%-28.9%) of neck relapse, raising the question of which patients should receive prophylactic neck treatment and which modality of treatment should be given to clinically negative neck lymph node maxillary SCC?

| Series                          | Year | n   | Maxillary tumour site | Positive involvement  | Nodal | Neck management                              | Regional relapse                          |
|---------------------------------|------|-----|-----------------------|-----------------------|-------|--|---|
| Jiang et al. [10]               | 1991 | 73  | 73                    | 6                     |       | N0: -17/67 ENI - 50/67 NNT N+ : Surgery+/-RT | N0: 11/50 NNT N+: 1/6                     |
| Paulino et al. [11]             | 1997 | 42  | 42                    | 4                     |       | N+: RT+/-surgery<br>N0: NNT                  | N0: 11/38 (9/11 ipsilateral)              |
| Kim et al. [3]                  | 1999 | 116 | 116                   | 12                    |       | N0: NNT                                      | 14/104 N0                                 |
| Le et al. [16]                  | 2000 | 97  | 97                    | 11 (9/58 SCC)         |       | RT   | 10  |
| Yagi et al. [26]                | 2001 | 118 | 118                   | 9                     |       | RT+surgery                                   | 9   |
| Snyers et al. [27]              | 2006 | 168 |                       | 18 (10/55 SCC)        |       | N0: NNT                                      | 11% of SCC (19 in maxillary sinus SCC)    |
| Cantù [6]                       | 2008 | 704 | 399 (156 SCC)         | 38 (33/399 maxillary) |       | N+: ND<br>N0: NNT                            | 66 (16/156 SCC)                           |
| Jang et al. [12]                | 2010 | 30  | 30                    | 0                     |       | N0: NNT                                      | 1   |
| Hinerman et al. [5]             | 2011 | 54  | 54                    | 9                     |       | 4 neck dissection<br>N0: 23 ENI              | 10<br>1/23 (N0 treated with ENI)          |
| Brown et al. [14]               | 2013 | 18  | 18                    | 1                     |       | N0: SND+/-RT                                 | 4   |
| Homma et al. [28]               | 2014 | 128 | 128                   | 28                    |       | N0: 83/100 NNT (0 ENI, 15 SND)               | 11  |
| Guan et al. [17]                | 2013 | 59  | 19                    | 18                    |       | N+: RT N0: 11/41 ENI                         | 7/59<br>N+:1/48<br>N0: - 6/4 -0/11 N0 ENI |
| Sakashita et al. [13]           | 2014 | 48  | 48                    | 0                     |       | NN0054                                       | 4   |
| Castelnaud-Marchand et al. [15] | 2016 | 104 | 104                   | 17                    |       | N0: 9 SND 28 ENI 17 SND +ENI 32 NNT          | 13  |

**Table 1:** Retrospectives series of maxillary sinus squamous cell carcinoma with neck management and regional relapses, NNT=No Neck Treatment, ENI=Elective Neck Irradiation, SND=Selective Neck Dissection, ND=Neck Dissection.

### The role of selective neck dissection

Regarding SND, there are very few reports in the literature. Brown et al. presented 18 patients with maxillary sinus SCC treated with this elective treatment [14]. Seventeen out of eighteen had no initial neck involvement. Of them, 13/17 underwent SND in which 1/13 had histologically positive nodes. Four out of eighteen patients presented regional relapse, in which 2/18 (11%) had SND. Regarding the low incidence of neck relapse, affecting only 2 patients with pathologically negative nodes, they concluded that SND did not improve disease control.

A recent French study reported 104 patients with sino-nasal SCC in which 76% were in the maxillary sinus. Eighty-seven of the 104 had N0 disease and only 9 presented regional relapse, principally associated with local relapse as well [15]. A better locoregional control (LRC), but not overall survival (OS), was found according to the management of the neck in favor of SND (94% vs. 47%; p=0.002). However, after excluding patients who had no resection of their primary tumour (n=23), there was no significant difference in LRC of patients with SND (n=27) as compared to others (n=37; p=0.07). None of the 24

patients who were treated with SND and had a pathologically negative neck (pN-) progressed in the neck.

The main risk of failure in these series was still primary site relapse, especially for patients with positive margins. Brown et al. reported 9 local relapses of the 10 patients who had histologically involved margins. No other recent studies exploring exclusive SND in N0 maxillary SCC patients were found. However, from the results of series reporting neck outcome without any prophylactic treatment or with SND only, it appears that regional relapse isn't frequent but associates with a significantly poor prognostic survival. Regional failure occurs more frequently in locally advanced disease, as in a recent report which showed regional failure of 28.4% in 139 patients with hard palate or maxillary SCC, associated with pathologic T classification, from 18.7% in pT1 disease to 37.3% in pT4 [5]. T stage was found to be an independent regional recurrence-free survival factor on multivariate analysis. Thus, SND can be proposed when primitive surgery is feasible, especially for high primary volume (T3-T4). Besides, it can be useful for lymph node staging and for the determination of radiotherapy dose and volume.

## The role of elective neck irradiation

The role of ENI, as exclusive neck management or after SND, in patients with N0 disease, remains unclear and controversial. Le et al. reported 5 year neck node relapse of 12% in 97 patients with maxillary cancer (58 with SCC), with higher incidence when histology was SCC. Eleven of the 58 SCC patients presented nodal involvement at initial work-up. None of the patients with N0 neck involvement at diagnosis, treated with ENI, presented neck relapse [16]. They reported a global risk of 28% of neck involvement at diagnosis or during follow-up. As in previous series, most of the regional relapse occurred in T3-T4 disease. Also, 5 year actuarial distant relapse rate was higher when patients presented neck failure, 81% vs 29% for those without neck failure. Significant higher risk of distant metastasis (DM) was estimated in patients with nodal neck failure in multivariate analysis with a hazard Ratio of 4.5 ( $p=0.006$ ). Only 1/23 patients with N0 initial maxillary sinus SCC treated with prophylactic ENI presented regional relapse in the series of Hinerman et al(5). In the Guan et al. series, none of the 11 patients with N0 paranasal sinus cancer treated with ENI had neck relapse, whereas 6/35 (17.1%) of N0 patients who did not receive any neck prophylactic management did [17].

The recent study of Sakashita et al. showed 4/48 (8.3%) late neck recurrences of 48 patients with N0 maxillary sinus SCC who were treated with superelective intra-arterial chemoradiotherapy without prophylactic neck irradiation, in which 47/48 had stage T3-T4 [13]. Of them, three underwent salvage neck dissection and survived, and one didn't undergo salvage dissection due to DM. They reported a mortality rate of 2% (1/48) from regional disease.

In the Castelnau-Marchand et al. study, of the 87 patients with N0 paranasal sinus SCC, including mostly maxillary sinus SCC primitive sites, neck management consisted in 10/87 (11%) of SND alone, 28/87 (32%) of ENI alone, 17/87 (20%) of an association of SND and ENI, and the 32/87 (37%) left ones did not have any prophylactic neck management(15). Among the 27 patients who underwent SND, 3/27 (11%) had pathologically positive nodes. Eight out of 87 (9%) patients had regional relapses, in which 6/8 were associated with local failure (2 of them with DM). No significant difference of OS neither LRC was found according to the management of the neck.

In a recent meta-analysis with a total of 129 patients with N0 SCC maxillary sinus, including most of the series presented in our review, ENI was considered as a significantly favourable factor of neck nodal recurrence (OR=0.16; 95% CI: 0.04-0.67;  $p=0.01$ ), compared to management by observation [18]. Considering these results, the prophylactic treatment, SND and/or ENI was recommended in the N0 neck, especially for locally advanced maxillary sinus SCC (T3-T4) where probability of occult lymph node metastasis is >10-20% [19].

## Radiation Techniques and Volumes

### Between outcome and toxicity: From 3D-CRT to IMRT

Post-operative or exclusive head and neck cancer radiotherapy induced substantial toxicity, especially xerostomia, taste loss and alteration of quality of life, with two-dimensional and even with 3D-conformal radiotherapy (3D-CRT). This morbidity is largely augmented when concomitant chemotherapy and neck irradiation are associated [20]. As a result, neck irradiation was often substituted by neck dissection, without confirmation of any advantages in outcome. In the French series where 90 patients received neck irradiation, 75/90 (83%) were treated with 3D-CRT and only 15/90 (15.7%) with IMRT

[15]. For the full population, grade 3 radiomucositis, radiodermatitis and dysphagia were found in 22%, 10% and 21%, respectively. No severe late toxicity was reported.

Intensity-modulated radiotherapy (IMRT) significantly improved dose distribution over 3D-CRT in head and neck cancer, especially when neck irradiation was associated, and reduced acute neck toxicity [21]. As shown in previous series, due to the low incidence of this disease, there is no randomized clinical trial comparing 3D CRT to IMRT in this particular site. However, Suh et al. recently reported, retrospectively, a better 3 year locoregional recurrence-free survival of 89.2% vs 59.5% ( $p=0.035$ ) with IMRT vs 3D-CRT in 54 patients with maxillary sinus carcinoma, and less toxicity with IMRT [22]. Grade 3 radiomucositis occurred in 31% vs. 0% in 3D-CRT and IMRT, respectively. Grade 2 xerostomia was observed in 9% vs 5%, respectively. These results can be explained by important modification of volume feasible with IMRT, offering higher coverage of primary tumour, which results in better locoregional control. They concluded that IMRT should be privileged over 3D-CRT in maxillary sinus cancer due to proximity of critical organs to the tumour and to improvement of dose distribution, sparing organs at risk.

### Doses, levels and side of neck irradiation

**Doses:** The most widely used prophylactic dose in N0 neck for maxillary sinus SCC is 50-54 Gy. However, as ENI is controversial due to the low incidence of neck relapse, the necessity to reduce post-radiotherapy toxicity is essential. Nevens et al. explored the effect on loco-regional control and toxicity of a reduction of dose of ENI from 50 Gy to 40 Gy with IMRT in 200 patients with head and neck cancer [23]. They reported no significant difference in 2-year disease control and survival between the two groups with a local failure rate of 14.1% vs 14.4% in the 40 Gy and 50 Gy arms, respectively; and regional failure rate of 13.0% and 5.5% ( $p=0.08$ ), respectively. Significantly less salivary gland toxicity was found in the 40 Gy arm. They suggested that dose de-escalation to the ENI volume in head and neck cancer could be an option to decrease morbidity without compromising disease control or survival.

**Levels and sides in N0 disease:** In the Le et al. series, they found that 84% of the neck relapses occurred in the ipsilateral side and were mostly limited to levels I, II and then III [16]. Ipsilateral levels Ib and IIa were also the most common sites of nodal recurrence in the Guan et al. series [17]. Suh et al. reported 12 regional recurrences, which occurred in the ipsilateral levels I, II and III in 3, 6 and 2 relapses, respectively, and only one contralateral relapse in the level II [22]. As well, in the French study, neck relapse was ipsilateral for 4 patients, bilateral for 3 and contralateral for one [15]. Most frequent levels were ipsilateral levels II, III (always associated with level II relapse), and Ib. From these retrospective series, most authors suggested that the prophylactic neck volume should include ipsilateral levels Ib, II +/- III for patients without clinical lymph node involvement [24,25].

## Conclusion

Neck failure remains an independent poor prognostic factor in maxillary sinus SCC. Prophylactic neck management, whether performed by SND or ENI, seems to improve locoregional control over active monitoring. SND may allow an increase of LRC and a better detection of occult cervical positive LN in order to propose selective post-operative radiotherapy. ENI is still controversial, but considering recent publications, it could be proposed in selected patients, especially

with T3-4 stage disease and when SND has not been performed. Volumes of ENI could include ipsilateral level II, +/- Ib and III or bilateral neck, according to the primary tumour extension. IMRT should be considered whenever feasible to reduce toxicity.

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