

Management of the Clinically Negative Neck in Early Squamous Cell Carcinoma of the Oral Cavity

Scharukh Jalisi, MD

*Department of Otolaryngology-Head and Neck Surgery,
Vanderbilt University Medical Center, S-2100 Medical Center North,
Nashville, TN 37232, USA*

Epidemiology

Oral cavity squamous cell carcinoma is the sixth leading cause of cancer worldwide [1]. It accounts for 0.6% to 5% of all cancers in Europe, United States, and Australia, respectively, but up to 45% of cancers in India [2]. It mostly affects males, but its incidence is growing among females. It usually occurs in the seventh decade of life. The most common causative factors associated with squamous cell carcinoma of the oral cavity are alcohol and tobacco abuse. Betel nut and tobacco chewing are responsible for the high incidence in the Indian subcontinent.

Background

The most important prognostic factor in the management of oral squamous cell carcinoma is the status of the cervical lymph nodes [3]. The presence of metastasis to cervical lymph nodes can reduce the cure rate by 50%. Historically the management of the clinically negative (N0) neck has been controversial. Since its description in 1906 by Crile [4] and its routine use by Martin [5], radical neck dissection was the main therapy for any cervical lymph node metastases from head and neck squamous cell carcinoma (HNSCC). The routine use of this operation was questioned and then modified by Bocca et al [6] and Byers [7], especially in patients with limited neck disease and those with clinically negative necks.

E-mail address: scharukh.jalisi@vanderbilt.edu

Currently the treatment dilemma that most head and neck oncology surgeons face is the treatment of the N0 neck in oral cavity squamous cell carcinoma. Three treatment options are available:

- Observation with therapeutic neck dissection once regional metastases become apparent
- Elective neck irradiation
- Elective neck dissection

These multiple treatment options, along with different treatment modalities available for the primary cancer, make the neck treatment of early-stage oral cavity squamous cell carcinoma controversial.

Anatomy

The oral cavity extends from the skin-vermillion junction of the lips to the junction of the hard and soft palate superiorly and to the line of the circumvallate papillae inferiorly. The subsites are [8]

- Mucosal lip
- Buccal mucosa
- Lower alveolar ridge
- Upper alveolar ridge
- Retromolar trigone
- Floor of the mouth
- Hard palate
- Anterior two thirds of the tongue (oral tongue)

Management issues and options

Some of the questions that arise when treating an N0 neck in squamous cell carcinoma of the oral cavity are

- Is there any noninvasive or invasive modality to assist in diagnosing cervical lymph node metastasis?
- Should the neck be treated now or observed?
- Are there prognostic factors that can guide decisions on whether or not to treat the neck?
- What modality should be used to treat the neck?
- Is there an optimal surgical approach to treat the neck?

Diagnostic modalities

Ideally, the decision about treatment of an N0 neck would be simplified if there were a highly accurate, noninvasive diagnostic modality that could identify metastatic lymph nodes. Studies have shown that the sensitivity, specificity, and accuracy of detection of neck metastases by clinical examination are 70%, 65%, and 68%, respectively. Stuckensen et al [9]

compared the usefulness of PET with ultrasound, CT, and MRI in detecting lymph node metastases. Ultrasound had the highest sensitivity (84%), and PET had the highest specificity (82%) among these modalities. Hence, it was concluded that noninvasive diagnostic modalities were not as accurate as histologic sectioning of lymph nodes. Other studies have shown that the detection rate of cervical adenopathy increases from 75% with physical examination alone to 91% when physical examination is combined with CT [10]. Compounding this problem, approximately 8% to 10% of oral and oropharyngeal squamous cell carcinomas have micrometastases to the cervical lymph nodes. These micrometastases can be only 3 mm to 6 mm in diameter, making them pathologically negative during preoperative work-up using current criteria [11–13].

In oral cavity squamous carcinoma, invasive diagnostic modalities to assess lymph node metastasis include a staging neck dissection (ie, supraomohyoid neck dissection [SOHND]). Davidson et al [14] estimated the accuracy of SOHND in detecting regional metastases to be 98% with a sensitivity of 95% and specificity of 100%, making it currently the best modality for detecting cervical metastases.

Prognostic factors

There is voluminous literature discussing different factors that effect prognosis in oral cavity carcinoma. The key factors are presented here.

Tumor size

Several studies have shown that increasing tumor size leads to decreased survival. The 5-year survival rates for oral cavity squamous cell carcinoma are 91% for T1 disease, 63% for T2 disease, and 60% for T3 disease. In addition a study by Tytor et al [2] involving 176 patients with oral cavity carcinoma showed that the rate of cervical lymph node metastasis was 14% in patients with T1 tumors, 37% in patients with T2 tumors, and 57% in patients tumors greater than 4 cm in diameter. On the other hand, reports by Rasgon [15] and Byers et al [16] did not show this correlation between the T-stage and cervical node metastasis.

Perineural invasion and intralymphatic tumor emboli

Perineural invasion is defined as tumor invasion of the perineural sheath or epineurium. Brown et al [17] demonstrated that regional metastatic disease developed in 71% of N0 patients who had perineural invasion versus 36% of N0 patients who did not have perineural invasion. This study also showed that in the presence of perineural invasion 2-year survival decreased from 82% to 52%. Lydiatt et al [18], in a study of 156 patients with stage I and II tongue cancer, found that local control rate at 5 years was 38% in patients with perineural invasion, versus 78% in patients without perineural invasion. Hence perineural invasion has been associated with decreased survival and with increased local recurrence necessitating more aggressive therapy.

Similarly, 88% of the patients who had intralymphatic tumor emboli in the N0 neck developed regional disease, versus 38% of patients who did not have such emboli [17].

DNA ploidy

In one study, bone invasion occurred in 68% of patients with DNA nondiploid tumors, versus 22% of patients with DNA diploid tumors [2]. Nodal metastases occurred in 54% of DNA nondiploid and 19% of DNA diploid tumors. Rasgon [15] and Mendelson et al [19] showed a relationship between differentiation grade and the rate of cervical lymph node metastases. Hence, discussion of the DNA diploid state and grade of the tumor with a pathologist is important in treatment planning.

Tumor thickness

In recent years the relationship of occult cervical lymph node metastasis with thickness of the tumor has been widely investigated.

Fukano et al [20] showed in 34 patients that cervical metastasis increased from 5.9% for tongue carcinomas less than 5 mm thick to 64.7% for tongue carcinomas more than 5 mm thick. Brown et al [17] noted that 38% of patients with tumor thickness less than 3 mm developed regional disease, compared with 41% of patients with tumor thickness of 3 mm to 7 mm and with 55% of patients with tumor thickness greater than 7 mm. He also showed that increasing tumor thickness is associated with greater perineural invasion. Fakhri et al [21] noted that in T1 and T2 squamous cell carcinoma of the oral tongue a thickness greater than 4 mm is associated with a greater risk of neck relapse. Another study noted that the rate of rate of occult cervical metastases increased from 7% to 30% when the thickness of the tumor was greater than or equal to 4 mm [22].

A study of 156 patients with stage I and II squamous cell carcinoma lesion of the floor of mouth demonstrated that cervical metastasis occurred in 2% of cases with thickness less than 1.5 mm, in 33% of cases with thickness of 1.6 mm to 3.5 mm, and in 60% of cases with thickness greater than 3.6 mm. The investigators concluded that elective neck dissection (END) should be undertaken in floor of mouth squamous cell carcinomas more than 1.5 mm thick [23].

Tumor thickness has also been shown to correlate with survival in several studies. In one such study [17], the 2-year survival rate was 94% for tumors less than 3 mm thick, was 69% for tumors greater than 3 mm but less than 7 mm thick, and decreased to 58% for tumors more than 7 mm thick. Similarly Urist et al [24] had shown improved survival in buccal cancer patients when thickness is less than 6 mm.

Extracapsular spread

The presence of extracapsular spread (ECS) further reduces survival. In a retrospective review by Alvi and Johnson [25] of N0 neck dissection

specimens, the occult metastatic rate was 34%, and ECS was noted in 49% of these specimens. In the presence of ECS the 2-year survival decreased from 47% to 31%. The authors recommended adjuvant therapy in the presence of ECS.

Hence, multiple factors that can affect the rate of cervical metastasis and survival from oral cavity cancer. It is important for the head and neck oncologic surgeon to be familiar with these factors to be able to provide patients the best counsel about the appropriate treatment modalities.

Observation versus elective neck treatment

There is great controversy regarding the optimal therapy for clinically negative necks. The proponents of observation cite the morbidity of END as a reason to observe. Another argument for close observation is that with close follow-up, any cervical metastasis can be detected early and then treated with adequate therapy. Moreover the occult metastatic rate to the neck from oral cavity cancer is 34% [3]. Hence, it is argued that nearly two thirds of the patients would be exposed to the morbidity of a neck dissection unnecessarily.

On the other hand Weiss et al [26] created a decision-tree analysis and concluded that observation is the preferred option when the probability of occult metastasis is less than 20% and elective neck treatment (irradiation or dissection) is preferred if the probability of occult metastasis is greater than 20%. In squamous cell carcinoma of the oral cavity the sites with a less than 20% occult metastatic rate to the neck are T1/T2 lip carcinomas, T1/T2 oral tongue carcinomas that are less than 4 mm thick, and T1/T2 floor of mouth cancers less than or equal to 1.5 mm thick.

The proponents of surgical intervention also note that removal of lymph nodes can be used as a staging procedure. If there is presence of extracapsular spread, the patient can be upstaged and receive more aggressive therapy early on rather than later when survival may be adversely affected. Andersen et al [27] demonstrated that 77% of patients with clinically N0 necks at initial observation had pathologically adverse findings at the time of neck dissection. Furthermore 49% of these patients had ECS, a poor prognostic factor. Hence, they argued for elective neck treatment (irradiation or neck dissection) in patients with N0 necks.

Another study comparing glossectomy and neck observation versus glossectomy and neck dissection for T1 and T2 squamous cell carcinoma of the oral tongue concluded that survival in the observation group was 33%, compared with 55% in the neck dissection group, and that locoregional control increased from 50% to 91% when neck dissection was performed. Again, the rate of ECS in this study was noted to be 58% in patients who were observed [18]. A similar study comparing 5-year survival in T1/T2 N0 squamous cell carcinoma of the oral tongue found that the survival rate decreased from 80.5% to 44.8% when a delayed neck dissection was

performed [28]. Kligerman et al [22] had shown that in early carcinoma of the oral cavity the addition of a SOHND increased 3-year survival from 49% to 72%.

Wendt et al [29] reported that, in 103 patients with T1 and T2 N0 squamous cell carcinoma of the oral tongue, neck recurrence occurred in 44% patients who received no radiation treatment to the neck, in 27% of those receiving less than 40 Gy to the neck, and in 11% of patients receiving more than 40 Gy to the neck.

In summary, although the decision to observe or treat the N0 neck is left to the choice of the patient and the head and neck oncologist, in oral cavity carcinoma the only clinically N0 necks for which observation is appropriate are those associated with T1/T2 lip carcinomas, T1/T2 oral tongue carcinomas that are less than 4 mm thick, and T1/T2 floor of mouth cancers less than or equal to 1.5 mm thick.

Elective neck dissection versus elective neck irradiation

Once the decision to treat the N0 neck has been made, there are two possible treatment modalities. The question then arises whether to irradiate the neck or to perform a surgical lymphadenectomy.

Mendenhall et al [30] showed that elective neck irradiation (ENI) reduced the neck failure rate in patients with controlled primary tumors and N0 necks from 18% to 1.9%. The dose of radiation varied from 50 Gy to 75 Gy in the upper neck and from 40 Gy to 50 Gy in the lower neck. Another study reported that ENI provided a 95% control rate for neck recurrences compared with 38% without ENI in T1 N0 squamous cell carcinoma of the oral tongue [31]. Hence, the neck recurrence rate can be extrapolated to be 5%, which is comparable to the 4% to 7% recurrence rate noted in elective neck dissection [32]. At the University of Virginia the preference is ENI for N0 necks [33].

The modality that is chosen to treat the primary cancer may also help in formulating a decision as to how to treat the neck. If primary radiation therapy is used, ENI can be performed. If the neck is going to be entered to remove the primary tumor, an END can be performed. Obviously, the risks of ENI and END need to be considered on an individual basis for each patient.

The argument for END is that it can be used as a staging procedure and hence help in determining the need for any future therapy. Also, the risk of a second primary tumor in treated cancers of the oral cavity is 4% to 6% per year [34]. Hence, using ENI in patients with early squamous cell carcinoma of the oral cavity may exhaust the use of radiation therapy as a treatment in the event of a future head and neck cancer. Other morbidities associated with ENI are xerostomia, dysphagia, greater oral passage time after radiation therapy, mucositis, pain, poor wound healing, increased complications if salvage surgery is performed, longer duration of therapy (up to

6 weeks), cost of travel, and time away from work. In a series of 85 patients treated for T1 and T2 N0 squamous cell carcinoma of the oral tongue, Al-Rajhi et al [35] demonstrated that the rate of neck recurrence was 35% in patients who were observed, 39% in patients who received ENI, and 19% in patients who received END. These investigators concluded that END is the modality of choice for treatment of the N0 neck. They used ENI with a total dose of 45 to 50 Gy, however, and showed no survival difference between the three groups.

Chow et al [36] demonstrated that after 5-year follow-up there was no statistical difference between ENI and END in regard to neck recurrence for cancers of the oral cavity, oropharynx, and larynx.

In summary the literature provides no clear-cut recommendation for using ENI or END to treat N0 necks. The most important factors in guiding this decision should be the patient's informed decision, physician and institution experience, risk of second primary occurrence in the future, and the modality chosen to treat the primary cancer.

Elective neck dissection—which surgery should be performed?

The lymph nodes at highest risk of occult metastases from oral cavity cancers are those at levels I, II, and III [3]. The metastatic rates to these sites are 58% (level I), 51% (level II), 26% (level III), 9% (level IV), and 2% (level V). There has been a long-lasting debate about the relative efficacy of SOHND and that of a classic radical neck dissection. Several studies have shown that there is no statistically significant difference in locoregional recurrence between a selective neck dissection and a radical neck dissection [32]. Byers et al [37] noted a skip metastasis rate of 15% to level IV in squamous cell carcinoma of the oral tongue and advocated that dissection of level IV should be included in a selective neck dissection. More recently it has been demonstrated that level IV need be dissected only if there are suspicious nodes in level II or III [38]. In conclusion, there is voluminous literature supporting the use of selective neck dissection for surgical treatment of N0 necks in oral cavity carcinoma. This procedure has relatively low morbidity when compared with the classic radical neck dissection.

Combined-modality treatment

In several situations postoperative radiation or salvage surgery is necessary. Several authors [18,32,39] and the Head and Neck Society [40] guidelines recommend the use of postoperative radiation therapy when there are perineural, intravascular, and intralymphatic tumor spread, positive microscopic margins, more than two histologically positive lymph nodes, multiple positive lymph nodes, extracapsular spread, and DNA nondiploid tumors.

Management of the contralateral N0 neck

Another issue of concern is the treatment of the contralateral N0 neck. A study showed that there was a 14% incidence of involvement of contralateral neck nodes regardless of tumor stage. The Head and Neck Society recommends the treatment of the contralateral nodes if the primary oral cavity cancer is midline, bilateral, along the tip of the tongue, or approaches or crosses the midline.

Future directions

The difficult choices that need to be made and discussed with patients would be easier if there were a noninvasive technology that could correctly identify metastatic lymph nodes in a N0 neck. Currently proton magnetic resonance spectroscopy is being investigated for this purpose [41,42].

In squamous cell carcinoma, sentinel node biopsy has been used with mixed results. It has been used in melanoma of the head and neck. Koch et al [43] concluded the difficulty with this method for oral cavity squamous cell carcinoma. Alex et al [44], on the other hand, showed that in eight cases sentinel node biopsy correctly identified the metastatic node in every case. Obviously more research, including large, prospective, randomized studies, is needed before this modality will be widely accepted in this realm.

Summary

1. Management of the N0 neck in squamous cell carcinoma of the oral cavity is controversial.
2. The N0 neck should be treated if the risk of occult metastasis is greater than 20%.
3. Sites where the neck can be observed are T1/T2 squamous lip carcinomas, T1/T2 oral tongue squamous carcinomas that are less than 4 mm thick, and T1/T2 squamous floor of mouth cancers less than or equal to 1.5 mm thick.
4. ENI and END seem to have comparable control rates (except in a study by Al- Rajhi [34]).
5. Ultimately the decision to treat the neck and the modality used depend on the patient's preference, physician and institution experience, the risk of a second primary cancer in the future, and the modality used to treat the primary cancer.
6. Development of future technologies and large, randomized, prospective trials of these technologies will shape the future of this treatment dilemma.

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