

## ONCOLOGY

# Elective neck dissection in oral carcinoma: a critical review of the evidence

## *Lo svuotamento laterocervicale elettivo nel carcinoma orale: revisione critica dell'evidenza*

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## SUMMARY

More than 50% of patients with squamous cell carcinoma of the oral cavity have lymph node metastases and histological confirmation of metastatic disease is the most important prognostic factor. Among patients with a clinically negative neck, the incidence of occult metastases varies with the site, size and thickness of the primary tumour. The high incidence rate of occult cervical metastases (> 20%) in tumours of the lower part of the oral cavity is the main argument in favour of elective treatment of the neck. The usual treatment of patients with clinically palpable metastatic lymph nodes has been radical neck dissection. This classical surgical procedure involves not only resection of level I to V lymph nodes of the neck but also the tail of the parotid, submandibular gland, sternocleidomastoid muscle, internal jugular vein and spinal accessory nerve. It is a safe oncological surgical procedure that significantly reduces the risk of regional recurrences, however it produces significant post-operative morbidity, mainly shoulder dysfunction. Aiming to reduce morbidity, Ward and Roben described a modification of the procedure sparing the spinal accessory nerve to prevent post-operative shoulder morbidity. Several clinical and pathological studies have demonstrated that the pattern of metastatic lymph node metastases occurs in a predictable fashion in patients with oral and oropharyngeal carcinoma. The use of selective supraomohyoid neck dissection as the elective treatment of the neck, in oral cancer patients, is now well established. However, its role in the treatment of clinically positive neck patients is controversial. Some Authors advocate this type of selective neck dissection in patients with limited neck disease at the upper levels of the neck, without jeopardizing neck control. The main factors supporting this approach are the usually good prognosis in patients with single levels I or II metastasis independent of the extent of neck dissection, and the low rates of level V involvement in oral cavity tumours. Furthermore, the high incidence of clinically false-positive lymph nodes in oral cavity cancer patients is well recognized. In selected cases, supraomohyoid dissection could be extended to level IV, and followed by radiotherapy when indicated. Several reports have confirmed the usefulness of minimally invasive sentinel lymph node biopsy in melanoma and breast tumours. However, only preliminary data testing the feasibility of the method exist regarding the management of oral and oropharyngeal squamous cell carcinoma. The complexity of lymphatic drainage and the presence of deep lymphatics of the neck make application of this method difficult. This attractive concept has recently been explored by several investigators who examined the feasibility of identifying the sentinel lymph node in primary echelons of drainage from oral cavity squamous carcinoma. The current knowledge of sentinel lymph node biopsy does not allow avoiding the indication of elective neck dissection in clinical practice. Sentinel lymph node biopsy cannot be considered the standard of care at this time. However, there are multi-institutional clinical trials testing this approach. Management of occult neck node metastasis continues to be a matter of debate. The role of imaging methods such as ultrasound-guided needle biopsy, sentinel node biopsy and positron emission tomography-computed tomography are still being evaluated as alternatives to elective neck dissections. Whether one of these techniques will change the current management of cervical node metastasis remains to be proved in prospective multi-institutional trials.

KEY WORDS: Oral cancer • Treatment • Neck dissection • Lymph nodes • Elective neck dissections

## RIASSUNTO

Oltre il 50% dei pazienti con carcinomi del cavo orale ha metastasi linfonodali ed il coinvolgimento dei linfonodi rappresenta il più importante fattore prognostico. L'incidenza delle metastasi linfonodali dipende dalla sede, dalle dimensioni e dallo spessore della neoplasia. Questa incidenza elevata di metastatizzazione regionale è il principale argomento a favore della linfoadenectomia elettiva. Nei pazienti con metastasi linfonodali clinicamente evidenti la linfoadenectomia classica (svuotamento laterocervicale radicale) prevede non solo l'asportazione dei livelli I-V ma anche importanti strutture del collo quali il polo inferiore della parotide, la ghiandola salivare sottomandibolare, il muscolo sternocleidomastoideo, la vena giugulare interna ed il nervo spinale. Questa tecnica oncologicamente affidabile è tuttavia gravata da importante morbidità, particolarmente nella funzionalità di movimenti della spalla, che incide pesantemente sulla qualità della vita. Per ridurre questi effetti collaterali Ward and Roben hanno proposto varianti tecniche più conservative, ad esempio la preservazione del nervo spinale. Numerosi studi clinici e patologici hanno evidenziato la sostanziale prevedibilità della diffusione linfatica nei carcinomi orali ed orofaringei. Sulla base di questi studi sono state introdotte le linfoadenectomie selettive, che si propongono di ottenere migliori risultati funzionali a parità di risultati oncologici rispetto alla chirurgia radicale. Il razionale di queste linfoadenectomie è ampiamente condiviso, mentre ne è discussa l'estensione sia nei pazienti con metastasi linfonodali (linfoadenectomia sovrao-moioidea oppure radicale) sia in quelli cN0 (livelli I-IV, I-III ovvero linfoadenectomie superselettive). Lo studio del linfonodo

*sentinella ha introdotto sicuramente importanti conoscenze, tuttavia questa tecnica non può ancora essere considerata uno standard di cura e va eseguita solo nell'ambito di studi clinici controllati. Importanti contributi nel riconoscimento dei linfonodi con micrometastasi (cN0 pN1) potrebbero venire dalle nuove metodiche di diagnostica per immagini. La loro affidabilità va comunque testata nell'ambito di ricerche multidisciplinari e multicentriche.*

PAROLE CHIAVE: Carcinoma orale • Terapia • Linfadenectomia laterocervicale • Linfonodi • Linfadenectomie selettive

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## Introduction

Neck metastasis is the most important prognostic factor in head and neck squamous cell carcinomas (SCC) <sup>1-3</sup>. On account of this widely demonstrated fact, management of neck disease in head and neck cancer has been considered one of the most important aspects of treatment. Nobody can deny the important effect of therapeutic neck dissection in the prognosis of head and neck cancer patients. However, the role of elective neck dissection has been a matter of discussion, since its introduction as routine practice <sup>4-7</sup>.

Of the head and neck diseases, oral cancer has been the most widely studied tumour as far as concerns elective neck dissection. However, the amount and quality of information currently available does not offer a definitive answer to the question of the prognostic effect of elective neck dissection. Furthermore, the recent introduction of sentinel lymph node biopsy in the diagnosis and treatment of head and neck cancer, has brought back the old question regarding the clinical usefulness of elective neck dissection.

Aim of this article is to review the evidence available concerning the usefulness of elective neck dissection.

## Historical landmarks

The first description of modern neck dissection has traditionally been considered the publication by George Crile, in 1906, in his classic paper with 132 patients, with 8% mortality and 3-year survival of 38% <sup>8</sup>. Of these 132 dissections, 86 were classified as other types of dissection different from en bloc radical neck dissection. Probably, this group of neck dissections would correspond to the modern selective neck dissections. However, there are too few details to allow recognition of the type of procedure. Ward <sup>9</sup>, in 1951, was one of the first to suggest the possibility of making a formal selective neck dissection sparing the spinal accessory nerve. At that time, the technique of neck dissection included the en-bloc resection of the spinal accessory nerve, the jugular vein and the sternocleidomastoid muscle, and in some cases, the resection of the vagus nerve. However, this tendency was not widely accepted, until the 1980's decade, when results of studies comparing radical and modified radical neck dissections demonstrated the same oncologic results with a higher functional compromise and shoulder pain for patients submitted to radical procedures. This change of surgical technique had an important relationship with elective neck dissection, because it is intrinsic in the philosophy of a preventive treatment, to make it the less invasive possible without losing oncologic results.

## Indications

Classically, neck dissection has been divided into: a) therapeutic, when it treats lymph node metastases found during physical exam or imaging studies; b) opportune, when the approach for exposure and resection of a malignant primary tumour is through the neck; c) elective, when lymph node compromise is not found clinically or by imaging, but the risk of microscopic metastases is higher than the risk associated with addition of a surgical procedure and its morbidity. In principle, the indication of neck dissection in oral cancer is a problem of risk-benefit evaluation between the probability of neck metastases, the probability of complications associated with neck dissection and the possible prognostic influence of late diagnosis of metastasis during follow-up. If the probability of neck metastases is high, to make a neck dissection with its intrinsic morbidity has the same effect as therapeutic dissection, decreasing the risk of regional recurrence. However, if the probability of neck metastases is low or nil, neck dissection simply acts as an overtreatment, where the morbidity of the neck procedure only offers a decrease in quality of life and functional deficits. Finally, the problem would be solved if it were possible to predict the risk of neck metastases. However, this type of prediction has been difficult to introduce and apply in clinical practice.

## Diagnosis of metastatic lymph nodes

One of the first and most important problems concerning elective neck dissection indication is related to the diagnostic methods to classify a patient as neck positive or negative. The clinical examination, upon which the TNM classification is based, is far from being a perfect examination. Merritt et al. <sup>10</sup>, in a systematic review of studies comparing palpation with computed tomography (CT), found a sensitivity of 75% and 83% and a specificity of 81% and 83% for palpation and CT, respectively. Giancarlo et al. <sup>11</sup> comparing palpation with ultrasonography (US) found no differences between the methods, and palpation had a sensitivity of only 82% and specificity of 80%. Akoglu et al. <sup>12</sup> studied 23 patients and found a sensitivity of palpation of 59.2% and a specificity of 93%, widely surpassed by operative characteristics of CT (sensitivity 78%, specificity 80%) and US (sensitivity 80%, specificity 59%). Haberal et al. <sup>13</sup> studied 48 patients and found a sensitivity of 64%, 72% and 81% and a specificity of 85%, 96% and 96%, for palpation, US and CT. Even more, clinical examination does not improve during intra-operative evaluation. Rasseckh et al. <sup>14</sup>, in 79 patients, found a sensitivity of 41% and a specificity of 57% in N0 patients assessed intra-operatively. Finn et al. <sup>15</sup> analyzed 34 patients in whom surgeons had divided lymph nodes, intra-operatively, into

clearly benign, clearly malignant and suspect and correlated the clinical impression with pathological results. Sensitivity of macroscopic evaluation was 56% and specificity was 70%. Wein et al.<sup>16</sup>, in a study on 36 patients, with biopsy of suspicious lymph nodes, found a sensitivity of 41% with a specificity of 100%.

Addition of a new imaging method such as PET-CT has not clearly demonstrated better operative characteristics than its predecessors. Schoder et al.<sup>17</sup>, in a study on patients with oral tumours, assessing 36 necks, classified N0 by palpation and with negative CT and magnetic resonance imaging (MRI), PET-CT showed a sensitivity of 67% and specificity of 85%, which offer no advantages, as staging tools, in N0 patients. Other imaging methods such as US and tomography showed a sensitivity of 72% and 81% and specificity of 96% and 95%, respectively. Ng et al.<sup>18</sup>, in a study on 134 patients classified N0, found a sensitivity of 51% for PET that increased to 57% when concomitant CT was performed and a specificity of 98%. Stuckensen et al.<sup>19</sup> studying 106 patients found a sensitivity of 70%, 84% and 66% and a specificity of 82%, 68% and 74% for PET, US and CT, respectively. At this point it is clear that clinical and imaging studies are not sufficiently sensitive to modify the indication of elective neck dissection. Nonetheless, some authors have suggested that, theoretically, patients with negative results using the most accurate imaging studies, such as CT or PET-CT, could be candidates to a wait-and-see policy, avoiding neck dissection<sup>20</sup>. However, this leads to discussion of the second point, the probability of lymph node metastases in relation to the features of the primary tumour.

### Risk factors of lymph node metastasis

As clinical examinations and imaging studies are not very accurate, interest has been focused on the prediction of the risk of neck metastases. Many studies have been published attempting to predict this risk. However, the main difficulties encountered in these studies are related to the impossibility to apply the results pre- or intra-operatively to perform or avoid neck dissection, since it is impossible to analyse the pathological features of the primary tumour intra-operatively and, moreover, the designed indexes are of poor discriminatory value.

Shear et al.<sup>21</sup>, in almost 900 patients, identified size, site and differentiation grade as predictive factors. However, they defined minor tumours, i.e., < 3 cm, a diameter with a high probability of metastases. Yamamoto et al.<sup>22</sup> found that type of tumour invasion was the most significant prognostic factor for the presence of lymph node metastases, Okamoto et al.<sup>23</sup> found that keratinization, number of mitoses, in addition to clinical factors were reliable to predict node metastases, Borges et al.<sup>24</sup> found perineural invasion and tumour thickness to be useful predictive variables while Martinez-Gimeno et al.<sup>25</sup> found microvascular invasion and tumoural inter-phase as predictive factors, besides other mentioned variables. However, many of these features can only be assessed in the final pathologic specimen<sup>26</sup>, therefore its practical application is limited. Moreover, most of these studies have not been widely validated in other tumour localizations, unlike those of original studies or in other populations, thus reducing its generalizability.

### Elective neck dissections

As these two alternatives are not useful, in clinical practice, to select the better candidates for elective neck dissection, the only remaining way to demonstrate the usefulness of elective neck dissection was by making a randomised controlled trial (RCT). However, it is not as easy as it appears. To date, only 3 RCTs have been performed. This small number results from various difficulties, such as the usefulness of elective neck dissection perceived by surgeons, the obvious difficulty of salvage surgery in a neck with macroscopic metastases in comparison with one without enlarged lymph nodes and the low long-term morbidity reported for elective neck dissection.

Vandenbrouck et al.<sup>27</sup> studied 75 patients with oral cavity tumours randomized to an elective radical neck dissection or wait-and-see policy followed by therapeutic neck dissection. The rate of positive lymph nodes was 49% in the dissection group and 47% in the observation group and the survival curves did not show statistically significant differences. However, the sample size was small and two patients in the observation group were not suitable for salvage surgery.

Later, Fakhri et al.<sup>28,29</sup> reported a RCT with patients with oral tongue tumours demonstrating a better overall and disease-free survival for the group of elective neck dissection. This study while offering a long follow-up, still suffers from a small sample size. As important data, they found that benefits of elective neck dissection were more evident in patients with tumours deeper than 4 mm. Finally, Kligerman et al.<sup>30</sup> in a RCT with 67 patients, found a recurrence rate of 42% in the group of observation vs. 24% in the group of elective neck dissection and a 3.5-year disease-free survival rate of 49% vs. 72%, respectively.

Results from these studies, classified as the best available evidence, suggest that elective neck dissection offers advantages in terms of overall, cancer specific and disease-free survival.

Although these results are not conclusive on account of the methodological weakness already mentioned, head and neck surgeons still maintain a policy of active treatment, offering elective neck dissection to N0 patients and with risk factors highly predictive of micrometastases.

With this in mind, the next question was the extension of the elective dissection. Classically, the procedure recommended was radical or radical modified neck dissection, based on preliminary results that showed a rate of 10-25% of metastases at level 4<sup>31</sup>. Other results supporting this strategy were related to the presentation of skip metastases. Skip metastases are defined as metastases that exceed the theoretical lymphatic drainage pattern for specific tumour sites. In the case of oral cavity tumours, the expected order of neck lymph metastases, would be levels I and II, first and after surpassing this barrier, the compromise of levels III, IV and V. The numbers of this type of metastases at level IV rises from 3% to 28%, depending upon the specific site of the primary tumour<sup>32-35</sup>. However, the results from our group, in a large case series of 212 patients with oral cavity tumours treated systematically with supra-omohyoid neck dissection (SOH), found a neck recurrence rate of only 6%<sup>36</sup>. These contradictory results led us to design and perform a RCT comparing elective SOH with modified radical neck dissection in patients with oral cavity tumours<sup>37</sup>. This study clear-

ly demonstrated that the rate of neck recurrence and overall survival was not statistically different between groups, with a dramatic decrease in local complications rate and much better aesthetical and functional results. Since then, it is our policy to perform selective elective neck dissections with SOH or extended SOH neck dissection including level IV, only for patients with macroscopic suspicious nodes found during the surgical procedure.

A further study from our group demonstrated that the rate of ipsilateral recurrence was 4.5% and that almost 50% of these recurrences occurred inside the limits of previous neck dissection, thus supporting the safety of selective neck dissection<sup>38</sup>.

## Sentinel lymph node dissection

Finally, although all these strategies have attempted to avoid unnecessary neck dissections, the number of negative elective neck dissections could still be as high as 80%. The recent introduction of sentinel lymph node biopsy in oral

cavity tumours, used to better select candidates for neck dissection, appears to be a good alternative<sup>39,40</sup>. Results available from various studies, have shown good sensitivity and specificity, but this technique is still considered investigational and only a few groups have obtained the training curve necessary to apply it in clinical practice. Some practical problems such as shadow images and non sentinel lymph node detection or abnormal drainage patterns are difficulties that need to be overcome before this new technology can be widely applied in everyday clinical practice<sup>41</sup>.

## Conclusion

The evidence available suggests a protective effect of elective neck dissection for patients with oral cancer. It is important to validate the results of the most recent studies applying new technologies, such as PET-CT and sentinel lymph node biopsy, in larger populations and design RCTs comparing these strategies to define which is the best diagnostic and treatment approach.

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