REVIEW

Role of sentinel lymph node biopsy in oral cancer

Il ruolo del linfonodo sentinella nel carcinoma del cavo orale

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Key words

Squamous cell carcinoma • Oral cavity • Nodal metastases • Sentinel node

Parole chiave

Carcinoma squamoso • Cavo orale • Metastasi linfonodali • Linfonodo sentinella

Summary

Squamous cell carcinoma of the oral cavity represents about 2% of all malignant neoplasms and 47% of those developing in the head and neck area. The tongue is the most common site involved, and this incidence is increasing mainly in young people, possibly related to human papilloma virus infections. Prognosis depends on the stage: the 5-year survival rate of tongue squamous cell carcinoma, whatever the T stage, is 73% in pN0 cases, 40% in patients with positive nodes without extracapsular spread (pN1 ECS-), and 29% when nodes are metastatic with extracapsular spread (pN1 ECS+: $p \geq 0.0001$). Nodal micrometastases (cN0 pN1) are found in up to 50% of cN0 tongue squamous cell carcinoma patients operated on the neck. At present, no clinical, imaging staging modalities or biological markers are available to diagnose nodal micrometastases. The sentinel node biopsy has been tested since 1996 in order to find a solution to this problem. The sentinel node is the first node reached by the lymphatic stream, assuming an orderly and sequential drainage from the tumour site, and should be predictive of the nodal stage. According to the literature, sentinel node biopsy is a reliable technique in selected cN0 cases, but the procedure is still experimental and should not be performed outside validation trials. Successful application of sentinel node biopsy in the head and neck region requires surgical experience and specific technical devices, including pre-operative lymphoscintigraphy and intra-operative gamma-probe. Moreover, dynamic lymphoscintigraphy seems to be able to show the lymphatic stream from the primary tumour and could allow a selective neck dissection to be tailored thus reducing the related morbidity.

Riassunto

I carcinomi del cavo orale rappresentano circa il 2% di tutte le neoplasie maligne ed il 47% di quelle del distretto cervico-facciale. La lingua è la sede più coinvolta e l'incidenza dei carcinomi linguali è in aumento in tutto il mondo soprattutto nei giovani, probabilmente per la presenza di infezioni virali da papilloma virus. La prognosi di queste neoplasie dipende dallo stadio ed in particolare dallo stato dei linfonodi: la sopravvivenza a 5 anni è del 73% nei casi N0, del 40% in quelli con metastasi contenute nei linfonodi e del 29% nei casi con rottura della capsula linfonodale. Il problema clinico emergente è la diagnosi clinica pre-operatoria dei linfonodi micrometastatici. Infatti oggi non esiste alcun metodo clinico o per immagini e neppure markers affidabili per identificare questi linfonodi. Il linfonodo sentinella, ovvero il primo linfonodo raggiunto dal flusso linfatico partito dal focolaio tumorale, potrebbe risolvere questo problema diagnostico. La revisione della letteratura conferma questa ipotesi. Tuttavia questa tecnica deve essere ancora considerata sperimentale ed essere applicata solo nell'ambito di studi clinici controllati. Essa richiede esperienza chirurgica e necessita di una linfoscintigrafia pre-operatoria e di una gamma camera portatile per identificare nel corso dell'intervento il linfonodo sentinella. È anche allo studio una valutazione dinamica del flusso linfatico dalla neoplasia per identificare i livelli raggiunti in ogni singolo paziente: se questa ipotesi venisse confermata si potrebbe programmare una linfoadenectomia selettiva personalizzata.

Introduction

Squamous cell carcinoma (SCC) of the oral cavity represents about 2% of all malignant neoplasms and 47% of those developing in the head and neck area. The main risk factors are alcohol and tobacco, and their effects are multiplicative [1]. The tongue is the most common site involved, and this incidence is increasing particularly in young people [2-4], possibly related to human papillomavirus infections [5]. Prognosis depends on the stage: mortality ranges from 10% in stage I to 70% in stage IV, and the neck is a critical point [1 6 7]. The 5-year survival rate of tongue SCC, whatever the T stage, is 73% in pN0 cases,

40% in patients with positive nodes without extracapsular spread (pN1 ECS-), and 29% when nodes are metastatic with extracapsular spread (pN1 ECS+: $p > 0.00001$) [6]. The risk of neck metastasis depends on the site, size, grading, and depth of infiltration of the tumours [8]. Metastatic neck nodes (cN1) can be diagnosed pre-operatively in up to 95% of cases by both clinical and imaging evaluation such as ultrasonography (US), computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET) and fine-needle aspiration cytology (FNAC). These patients undergo neck dissection. Clinical diagnosis of negative nodes is difficult: nodal micrometastases (cN0 pN1) are found in up to 50% of cN0 tongue SCC patients operated on the neck [1 7 9-10]. Neck dissection is debated in these cases [11 12] because it could be an over-treatment in about half the patients, with a possible associated morbidity such as haemorrhage, nerve injury, pain, or lymphoedema [13 14]; on the contrary, the wait-and-see option should be considered an under-treatment in about half the cN0 patients, whose prognosis could be worsened by this non-aggressive approach [15-20]. Several non-randomised studies showed an improved survival in cN0 patients who underwent elective neck dissection [7 8 21-25]. The main problem is clinical detection of cN0 pN1 nodes. At present, no clinical, imaging staging modalities or biological markers are available to diagnose nodal micrometastases. Sentinel node biopsy (SNB) has been tested since 1996 in order to find a solution to this problem.

The sentinel node

The sentinel node is the first node reached by the lymphatic stream, assuming an orderly and sequential drainage from the tumour site, and should be predictive of the nodal stage [26]. SNB is now routinely used in clinical practice in order to avoid unnecessary lymph node removal in breast cancer and malignant melanoma, considering the high morbidity of axillary and groin dissection. In these patients, SNB is mainly a staging procedure for selecting those patients that could benefit from adjuvant treatments. On the contrary, neck dissection is a key part of the treatment of oral SCC, because patients die on account of regional recurrences. SNB, in oral SCC, is applied in many Institutions, in clinical trials, mainly to guide the decision-making on neck management in cN0 cases treated with a trans-oral approach [11 26-34]. Dynamic lympho-scintigraphy is under study in order to identify all the levels reached by the lymphatic stream from the primary tumour [35-37]: this information could allow a personalised selective neck dissection to be carried out.

Clinical experience of SNB in Head and Neck SCC

The first successful SNB in a head and neck SCC was performed, in 1996, by Alex and Krag on a patient with a laryngeal supraglottic carcinoma [38]. Two years later, Bilchik et al. included 5 patients with head and neck cancer in a report on SNB [39]. The techniques for the identification of sentinel node in head and neck cancer were widely debated. Pitman et al., injecting blue dye alone, were unable to find any sentinel nodes in the neck in 16 patients [17]. Koch et al., using a radiocolloid and intra-operative gamma probe, were only able to identify sentinel nodes in 2 out of 5 patients with oral and oro-pharyngeal SCC [40]. In 1999, Shoaib et al. suggested a SNB technique that was largely based on Morton's experience in melanoma: a) pre-operative lympho-scintigraphy; b) intra-operative blue dye; c) gamma probe localization [41]. In 2000, Chiesa et al. [26] investigated the reliability of SNB in predicting neck status in a homogeneous series of 11 patients with laterale T1-T2, N0, M0 tongue SCC who underwent ipsilateral neck dissection 30-40 days after primary surgery. These Authors concluded that the technique allows easy and safe identification of sentinel nodes and shows promise in guiding selective neck dissection. In June 2001, the conclusions of the 1st International Conference on SNB of head and neck SCC, held in Glasgow, underlined that results were significantly better in those centres that performed more than 10 cases a year: overall sentinel node identification was 98%, and sensitivity of the procedure was 90% [42]. Reliability of SNB was confirmed two years later, at the 2nd International Conference held in Zurich. Pooled data on 397 cN0 head and neck patients from 20 centres have been presented: the identification rate was 97% (range 90-100%), with a 96% (range 88-100%) negative predictive value of a negative sentinel node for the remainder of the neck using both pre-operative lympho-scintigraphy and intra-operative hand-held gamma probe [43]. The importance of pathological examinations of sentinel nodes, including step sectioning and immuno-histochemistry, has to be underlined for both micrometastases and Isolated Tumoral Cells (ITC) [43 44]. In 2002, Werner reported a sensitivity of 96.7% in a series of 90 patients with head and neck SCC, and stressed the role of serial sectioning and the need to remove all radioactive sentinel nodes [34]. The majority of series showed that the SNB technique usually removes 2-3 sentinel nodes. All required detailed pathological investigation [45 46]. The accuracy of SNB in patients with head and neck SCC is currently under investigation in a multicentre study sponsored by the American College of Surgeons Oncology Group, that compares the results of SNB with standard elective neck dissection [47]. Ross et al. re-

cently published preliminary results of a multicentre trial, based on the Canniesburn SNB protocol [48]. Six centres took part in the study and enrolled 134 T1/T2 cN0 oral and oro-pharyngeal SCC. Overall, 79 cases underwent SNB to stage the neck: a subsequent neck dissection was performed only in positive sentinel nodes, while 55 patients underwent elective neck dissection synchronous to the SNB. The overall identification rate was 93% and 42 cases (34%) were upstaged from cN0 to pN1. Identification of a sentinel node and sensitivity in SCC of the floor of the mouth were 86% and 80%, respectively, compared to 97% and 100% of the other sites. This difference could be related to the close proximity of the floor of the mouth to the draining nodal basin. This leads to difficulties in identifying and harvesting the sentinel node, even when using software masking techniques and lead shields. In conclusion, in our opinion, SNB is a reliable mini-invasive technique for detecting micro-metastatic nodes. Long-term oncological results of SNB followed by clinical follow-up in patients with negative histology are not yet available.

From SNB to Radio-guided Selective Neck Dissection

Neck dissection should be performed, also in cN0 and SNB-negative patients, when removal of the tumour or reconstructive surgical procedures for oral SCC include access through the neck [46]. In these cases, extension of surgery on the neck remains controversial; in particular, there is no agreement concerning which levels should be removed. To answer these issues, we evaluated whether lympho-scintigraphy can supply complete mapping of the lymphatic drainage before surgery, in order to plan reliable selective neck dissection tailored to each patient [37]. A low-weight tracer (colloidal sulphide particle size < 50 nm) was used to obtain this dynamic evaluation. Each cN0 patient received a maximum total activity of 40 MBq in 3 injections around the primary lesion, with an injected volume of 0.1 ml for each aliquot. After injection, patients were instructed to rinse their mouths thoroughly with tap water, to remove any residual radiocolloid. A dynamic acquisition was started after administration of colloids for 15 minutes in anterior view (30 seconds/frame). Static images of the head and neck in anterior and lateral views were acquired 30 minutes and again 2 hours after injection. A single photon emission tomography-computed tomography (SPECT-CT) was performed after delayed static images, in order to carefully localise the anatomical position of the lymph node(s) draining the injection area. This system allows simultaneous acquisition of anatomical and functional information. Post-operative images were compared with the pre-operative lympho-scintigraphy and the pathological findings. Preliminary results on 11 patients suggest that dynamic lympho-scintigraphy is able to supply complete mapping of the lymphatic drainage before surgery, thus making it possible to tailor a selective neck dissection for each patient, sparing healthy lymphatic tissue and reducing surgery-related morbidity [37].

Conclusion

Prognosis of oral SCC becomes worse as nodal involvement increases; in cN1 pN1 cases, neck dissection is potentially curative with a low morbidity. Management of cN0 patients remains controversial since up to 50% are cN0 pN1. SNB is a reliable technique in selected cN0 cases, but the procedure is still experimental and should not be performed outside validation trials [42 43]. Successful application of SNB in the head and neck region requires surgical experience and specific technical devices, including pre-operative lympho-scintigraphy and intra-operative gamma-probe. Moreover, dynamic lympho-scintigraphy would appear to show the lymphatic stream from the primary tumour and could thus allow selective neck dissection to be tailored reducing the related morbidity.

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