

An extended use of the sentinel node in head and neck squamous cell carcinoma: results of a prospective study of 100 patients

Impiego estensivo del linfonodo sentinella nel carcinoma squamocellulare della testa e del collo: risultati di uno studio prospettico su 100 pazienti

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Parole chiave

Carcinoma testa e collo • Metastasi linfonodali • Diagnosi • Linfonodo sentinella

Summary

Most studies concerning the use of the sentinel node technique in head and neck cancers have included clinically N₀ patients with primary early stage tumours of the oral cavity or upper part of oropharynx; furthermore, node sampling has been performed during the same session, but separately from the tumour. The perspective of avoiding unnecessary neck dissection, without increasing the risk of delayed diagnosis of lymph node metastasis, is rewarding, not only for early stage tumours of the oral cavity but also for tumours in advanced stages and/or at different anatomic sites. In the attempt to establish the reliability of extended use of the sentinel node technique, 100 consecutive untreated patients (from 1999 to 2002) with tumours located in the oral cavity, oropharynx, hypopharynx and larynx, at any T stage, entered the study. N+ patients with paramedian tumours and contralateral clinically negative nodes were also enrolled. After injection of the ^{99m}Tc albumin microcolloid, pre- and intra-operative evaluations with a γ -probe were done. N₀ patients (59) were submitted to mono- or bilateral selective neck dissection; the N+ patients (41) received homolateral dissection of all levels and contralateral selective dissection. An en bloc resection of the tumour was performed both in N₀ and N+ patients. In the N₀ group, histological examination showed no evidence of metastases in "hot" nodes in 34 patients and also the remaining nodes were negative. Metastases were found in one or more of the γ -probe positive nodes (14 cases), or in a closely located node at the same level (2 cases) or in a node close to a "hot" area of the submandibular salivary gland (1 case). In 8 patients, lymphoscintigraphy did not identify any sentinel node and histology of all lymph nodes was negative for metastases. In the N+ group, no metastases were found in the sentinel nodes of 21 patients and also the remaining nodes were negative; in 4 patients, metastases were found in sentinel nodes. In 16 patients, lymphoscintigraphy did not identify any sentinel node and histology of all lymph nodes was negative for metastases. In no patients were metastases found outside the level containing the lymph node identified as sentinel by the γ -probe. In conclusion, the strategy of the sentinel node is reliable, but, to be confirmed as a standard approach, it requires trials with a larger number of patients. The technique requires a multidisciplinary

Riassunto

Nella maggior parte degli studi clinici sul linfonodo sentinella, i tumori primitivi sono nel cavo orale o nella parte superiore dell'orofaringe, usualmente in stadi iniziali, N₀ e la dissezione linfonodale è eseguita nella stessa seduta separatamente dal tumore primitivo. La prospettiva di evitare uno svuotamento non necessario, senza aumentare il rischio di una diagnosi troppo tardiva di metastasi linfonodale, è attraente non solo per i tumori iniziali del cavo orale. Dal 1999 al 2002, sono entrati in questo studio 100 pazienti (pz) consecutivi non pretrattati, con lo scopo di verificare l'affidabilità di un impiego estensivo del linfonodo sentinella. I tumori, di ogni classe di T, erano localizzati nel cavo orale, oro- ed ipofaringe e laringe. Furono arruolati anche soggetti con N+ monolaterale e T paramediano: lo studio fu condotto per i linfonodi contralaterali clinicamente negativi. Dopo iniezione di albumina microcolloidale ^{99m}Tc, è stata eseguita valutazione intraoperatoria con un rilevatore gamma (γ -probe). Sono stati eseguiti svuotamenti selettivi nei lati senza evidenza clinica di metastasi linfonodali. I pz N+ hanno ricevuto svuotamento omolaterale di tutti i livelli e svuotamento selettivo contralaterale. Il tumore primitivo fu rimosso in monoblocco. Nel gruppo N₀ all'istologia in 34 pz non furono trovate metastasi nei linfonodi ipercaptanti ed anche gli altri linfonodi risultarono negativi, mentre furono identificate metastasi: in 1 o più linfonodi ipercaptanti (14 casi) o in un linfonodo limitrofo dello stesso livello (2 casi) o in un linfonodo vicino all'area ipercaptante della ghiandola salivare sottomandibolare (1 caso). Otto pz risultarono linfoscintigraficamente ed istologicamente negativi. Nel gruppo N+ non furono trovate metastasi nei linfonodi ipercaptanti di 21 pz ed anche gli altri linfonodi risultarono negativi; in 4 pz furono trovate metastasi nei linfonodi ipercaptanti. Sedici pz risultarono linfoscintigraficamente ed istologicamente negativi. In nessun pz furono identificate metastasi al di fuori del livello contenente il linfonodo ipercaptante identificato con la γ -probe. In conclusione, la strategia del linfonodo sentinella è affidabile, ma per essere considerata come approccio standard richiede conferme da studi clinici controllati con un numero elevato di pz; la tecnica richiede la costituzione di un gruppo multidisciplinare con un buon grado di comunicazione interna. Verosi-

and well “amalgamated” team. It may likely be used also in T3 and T4 oro-hypopharyngeal and laryngeal primary tumours and to determine surgical treatment of the contralateral neck in patients with N2a, N2b, N3 on T close to the midline.

Introduction

Between the “wait and see” policy and elective treatment of all N₀ neck patients, use of the sentinel node strategy and technique should be suggested as the appropriate tool to identify the small minority of patients (pts) with subclinical node metastasis, really needing treatment.

The majority of reports in the literature dealing with the use of the sentinel node technique, in head and neck squamous cell carcinoma (SCC)¹⁻¹¹, have usually included primary tumours, at early stages, located in the oral cavity or the upper part of the oropharynx, in N₀ pts; moreover, node sampling has been done during the same session, but separately from the primary tumour.

Other interesting fields of possible application of the sentinel node technique may be tumours at more advanced stages, or the treatment of the contralateral neck when the tumour is close to the midline and a homolateral lymph node metastasis is already present. Aim of this report is to discuss the vast experience gained from a prospective study from a single institution performed in the attempt to detect the reliability of extended use of the sentinel node technique.

Patients and methods

From May 1999 to December 2002, 100 consecutive untreated pts (78 male, 22 female, mean age 61 years, range 36-93), after having given informed consent, entered this prospective study, without modifying the ongoing treatment protocols. The site of the primary tumour was: oral cavity in 51 pts, oropharynx in 27, larynx in 12 and hypopharynx in 10. After work-up at baseline, including computed tomography scan of the whole neck, tumours were staged as follows: 15 T₁, 54 T₂, 17 T₃ and 14 T₄. There were 59 N₀ and 41 N+ pts (20 N₁, 6 N_{2a} and 15 N_{2b}). Pts with homolateral metastatic nodes had a paramedian SCC and the study was carried out for the contralateral, clinically negative, lymph nodes (LNs). After tracheotomy and induction of general anaesthesia, 0.4 ml of ^{99m}Tc albumin microcolloid (^{99m}Tc) (mean 37 MBq) were injected in 4 different points, 1 cm in depth, at 0.5 cm from the tumour margin. Adequate visualization was possible in all cases; in tumours of the tongue base, hypopharynx and larynx, a laryngoscope with a wide opening was particularly useful. Seven pts, all with tumour of the oral

milmente potrà essere impiegato anche nei T3 e T4, nei tumori primitivi dell'oro-ipofaringe e laringe e per decidere il trattamento chirurgico del collo controlaterale in pz con N2a, N2b, N3 e T paramediano.

cavity, were also studied with a γ -camera, the day before the operation. Preoperative evaluation, with a γ -probe, was done either through the intact skin or after raising the platysma skin-flaps and dissecting the anterior and medial surface of the sternocleidomastoid muscle from the superficial cervical fascia. Selective neck dissections were then performed on the sites without clinical evidence of node metastases (levels 1 to 3 in pts with oral cavity or oropharyngeal tumour, levels 2 to 4 in pts with laryngeal or hypopharyngeal tumours). A total of 128 selective neck dissections were evaluated: in the N₀ group, 33 pts with lateral tumour had homolateral selective dissection and 28 pts, with median or paramedian tumour, had bilateral selective dissection. The 39 N+ pts received homolateral dissection of all the levels and contralateral selective dissection.

Thread markers were applied to make the subdivision between levels easier. An en bloc resection of the tumour was performed, the specimen was placed on a sterile wrap and the levels were clearly marked with a pen, by the surgeon. The sentinel node(s) were again identified by the nuclear medicine specialist and the pathologist with the aid of a hand-held γ -probe detector (Navigator GPS, Gamma Positioning System, RMD, Watertown, MA, USA). Nodes are considered “positive” if the radioactivity level is at least 4 times the background level.

The pathologist isolated the sentinel node(s) and all the remaining identifiable LNs; all the isolated LNs were evaluated with an intra-operative cytological procedure. If the intra-operative cytopathologic examination revealed metastatic cells in one or more LNs, the dissection was completed with the remaining levels. The time for intra-operative pathological analysis ranged between 15 and 60 minutes. While waiting for the intra-operative reports (of margins and nodes), the surgical team began either the reconstructive or the simple closure procedure.

All the LNs examined intra-operatively and any remaining LNs dissected upon second inspection of the formalin-fixed residual selective neck dissection material were submitted for routine histological processing. Sentinel nodes and non-sentinel nodes were examined with routine haematoxylin & eosin (H&E) stain and, for each paraffin block of sentinel nodes, slides were prepared from three different levels. At each level, two sections were taken; one was stained with H&E and one was used for immunohistochemical analysis with AE1/AE3 anticytokeratin antibodies.

Results

N_0 - 59 PATIENTS

In this group, 1 to 8 sentinel nodes (total: 112) were identified in the lymphatic network of 50 pts; at histological examination in 34 pts, no metastases were found in the ^{99m}Tc + nodes and the remaining nodes were also negative. Metastases were found: in one or more of the sentinel nodes (14 cases) or in an adjacent node at the same level (2 cases); in another patient, a metastasis was found in a node adjacent to a ^{99m}Tc + area of the submandibular salivary gland (no

Allocation of the sentinel nodes, according to site of the primary tumour and neck level; allocation of the sentinel nodes and pN+ nodes according to site of T and neck level; upstaging of the neck, due to the sentinel node technique, according to site of T, and upstaging of the neck according to clinical class of – are shown, respectively, in Tables I, II, III and IV.

It is worthwhile pointing out that in 12 out of the 18 cases with metastatic ^{99m}Tc positive LNs, histopathological examination showed neoplastic depots only in the sentinel nodes and in 6 cases they were micrometastases. In two of these pts, both in the N_0

Table I. Allocation of γ -probe identified sentinel nodes by anatomical site of primary tumour and by neck level.

	I	II	III	IV	V
Oral cavity	16	45	9	–	–
Oropharynx	2	26	12	1	–
Larynx	–	9	13	2	–
Hypopharynx	1	6	3	3	–

Table II. Allocation of γ -probe identified sentinel nodes and pN+ nodes by anatomical site of primary tumour and neck level.

	I	II	III	IV	V
Oral cavity	1	6	3	–	–
Oropharynx	–	6	3	–	–
Larynx	–	3	2	–	–
Hypopharynx	–	–	–	–	–

lymph node uptake, numbered separately). These 3 latter cases were the only incorrect results in the entire series; in these pts, the site of the primary tumour and stage were: 1 pT2 N1 of the retromolar area, 1 pT4N1 of the lower gum and 1 pT3N1 of the base of the tongue. In the remaining 8 pts, lymphoscintigraphy did not identify a sentinel node and the histology of all the LNs was negative for metastases.

N+ 41 PATIENTS

In this group, examined for the contralateral clinically negative neck, 1 to 3 sentinel nodes (total: 24) were identified in the lymphatic network of 25 pts; at histological examination, the ^{99m}Tc + LNs of 21 pts were shown to have no metastases and also the remaining nodes were negative. In 4 pts, metastases were found in the γ -probe positive nodes (1 with a low level of ^{99m}Tc positivity). In 16 pts, lymphoscintigraphy did not identify any sentinel node and histology of all the remaining LNs was negative for metastases.

Table III. Upstaging of neck by site of primary tumour.

	Patients
Oral cavity	8
Oropharynx	7
Larynx	3
Hypopharynx	–

Table IV. Upstaging of neck by clinical class of primary tumour.

	Patients
T1	1
T2	10
T3	6
T4	1

group and presenting an oral cavity tumour, a sentinel node was identified only at level III and this was the only histologically positive node.

Moreover, no pts had microscopic tumour spread outside the level(s) containing the γ -probe identified sentinel node(s).

The pre-operative sentinel lymph node evaluation, compared to the later identification on the specimen, required a longer learning curve. False negative results were due to the closeness of the tumour site or, probably, to a slower ^{99m}Tc migration to the draining lymph node.

Discussion

We distinguish a strategy and a technique of the sentinel node. The strategy is based on the assumption that a primary tumour drains, at the beginning, to one or more LNs before disseminating to the remaining regional network. The corollary of this assumption is: if no tumour cells are identified in the sentinel node, the remaining LNs can be presumed to be free of disease. Complete reliability of this strategy will, of course, require further studies on a larger number of cases and with adequate follow-up.

For the technique of the sentinel node, a multidisciplinary team is mandatory: communication between the head and neck surgeon, pathologist and nuclear medicine specialist is crucial. It usually needs a learning period, but it is not challenging and may eventually become a standard approach.

To our knowledge, this is the first report on 100 consecutive pts who received a sentinel node evaluation in the context of an en bloc resection of the primary tumour (at any stage, any site) with the pertinent lymphatic network. The perspective of avoiding unnecessary neck dissection, without increasing the risk of late diagnosis of lymph node metastasis, is, in fact, exciting not only for early stage tumours of the oral cavity¹²⁻¹⁴. The results of a recent national survey in U.S.A. concerning the current management of T_3N_0 and T_4N_0 glottic carcinomas, show that a significant percentage of specialists who perform elective neck dissection, do it as radical neck dissection¹⁵.

On the other hand, there are no widely accepted guidelines regarding the treatment of the contralateral neck side when the tumour is close to the midline and homolateral lymph nodal metastasis is revealed. In these situations, use of the sentinel node technique on the contralateral neck may be helpful in deciding the treatment.

The majority of the γ -probe identified sentinel nodes (Table I) are located, as expected, at level II, followed by levels I and III for T of the oral cavity and level III for larynx and hypopharynx. Furthermore, the majority of pN+ nodes were at level II (Table II):

level I, even if closer to the oral cavity is less frequently the site of metastatic depots. Upstaging of a N_0 neck to N+ (Table III) occurred more frequently for T of the oral cavity and oropharynx, according to the consistency of these primary tumours, in the present series. Again, Table IV suggests that the frequency of node metastasis is not related to the size of T. Study of the distribution of the injected tracer, within the lymphatic network, is extremely interesting to better understand the metastatic pathway to the nodes: it is of educational significance for all members of the multidisciplinary team dealing with the sentinel node. Nevertheless, from a practical point of view, this type of study is, in our opinion, of little use since it shows only the level where the sentinel node is located. In the same way, the transcutaneous γ -probe examination is useful to indicate where the sentinel node should be sought, however to identify the sentinel node exactly among multiple closely located nodes, with the same macroscopic appearance, the intra-operative use of the γ -probe is, in our experience, mandatory.

In the present series, the accuracy of the γ -probe identification of the sentinel node was high, with 3/100 wrong results. A more complete reliability may be obtained dissecting not only the sentinel node but also the whole level with the target node. This γ -probe-guided super selective neck dissection with limited skin incision is possibly one of the next steps for a less invasive, specific patient-tailored means of treating the neck.

An interesting issue is how to consider the results when no sentinel node is identified: are these really non-draining nodes or did something go wrong during the procedure? This situation occurred in 24 of our pts and none of these pts presented lymph node metastases. Nevertheless, according to the literature, in this phase, which is still investigational, it is probably safer to judge these results as not reliable when deciding a therapeutic option.

A γ -probe machine is currently used by various surgical teams dealing with breast tumours and melanoma and other possible fields of application are under investigation. Therefore, it is possible to share the same device with other users, thus lowering the cost and optimizing the use.

Conclusions

From this experience, we learned that the strategy of the sentinel node is reliable; of course, to be confirmed as a standard approach, it requires prospective and, possibly, multicentric trials with a larger number of patients, homogeneously staged, treated and followed.

Moreover, the sentinel node would be used also in tu-

mours of the oropharynx, hypopharynx, and larynx and it may also prove useful in the choice of surgical treatment of the contralateral neck in N+ pts with tu-

mours close to the midline. The technique may be usefully employed within the framework of a multidisciplinary team.

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