Neck lymph node status is the most important factor for prognosis in head and neck squamous cell carcinoma. Sentinel node detection reliably predicts the lymph node status in melanoma and breast cancer patients. This study evaluates the predictive value of sentinel node detection in 50 patients suffering from pharyngeal and laryngeal carcinomas with a N0 neck as assessed by ultrasound imaging. Following 99m-Tc technetium nanocolloid injection in the periphery of the tumour intraoperative sentinel node detection was performed during lymph node dissection. Postoperatively the histological results of the sentinel nodes were compared with the excised neck dissection specimen. Identification of sentinel nodes was successful in all 50 patients with a sensitivity of 89%. In eight cases the sentinel node showed nodal disease (pN1). In 41 patients the sentinel node was tumour negative reflecting the correct neck lymph node status (pN0). We observed one false-negative result. In this case the sentinel node was free of tumour, whereas a neighbouring lymph node contained a lymph node metastasis (pN1). Although we have shown, that skipping of nodal basins can occur, this technique still reliably identifies the sentinel nodes of patients with squamous cell carcinoma of the pharynx and larynx. Future studies must show, if sentinel node detection is suitable to limit the extent of lymph node dissection in clinically N0 necks of patients suffering from pharyngeal and laryngeal squamous cell carcinoma.

Keywords: sentinel node; N0 neck; squamous cell carcinoma; larynx; pharynx; occult metastases

PATIENTS AND METHODS

This study was approved by an ethics committee and written informed consent was obtained from the patients at the beginning of therapy.

Patients

In 50 previously untreated patients (6 female, 44 male; age range: 33 – 79 years, median: 63 years) suffering from squamous cell carcinomas of the oropharynx (n=33), the larynx (n=14) and the hypopharynx (n=3) an intraoperative SN detection was performed. B-mode-ultrasound assessed a N0 neck in all 50 patients. Lymph nodes > 1 cm in diameter, lymph nodes with a spherical appearance or diffuse borders to the surrounding soft tissue were defined as criteria for malignancy in neck sonography. These cases required fine needle aspiration cytology and if they were preoperatively classified as N1-neck these cases were not enrolled in this study. Further details on the location and TNM-classification can be withdrawn from Table 1.

Methods

At the beginning of the surgery (tumour resection and neck dissection) the application of a total amount of 1.2 mCi Tc99m-nanocolloid, which was dissolved in 0.2 – 0.35 ml normal saline, was performed by intraoperative injections. This amount was chosen under the consideration of the special anatomical challenges in the lymphatic system of the upper aerodigestive tract, which is characterised by regional variation, but high density of lymphatics. An excessive amount of tracer substance leads to drainage into
of several neighbouring lymph node levels due to an unphysiological increase of the interstitial pressure. Before this background, it has to be pointed out, that more than 100 years ago Mascagni could show, that lymphatic fluids usually pass up to eight lymph nodes until they enter the blood vessels.

The tracer substance, which had been aspirated into a 1 ml syringe (Plastipak\textsuperscript{R}, Becton Dickinson, Madrid, Spain) was injected into four spots at the perimeter of the tumour under microscopic control. In cases of easily accessible SCCs of the oropharynx a hypodermic 24 Gauge needle of 25 mm length (Microlance\textsuperscript{R}, Becton Dickinson, Drogheda, Ireland) was used. Laryngeal and hypopharyngeal carcinomas were exposed via rigid endoscopy in general anaesthesia. The tracer substance was then injected under microscopic control into the perimeter of the tumour, using a 23 Gauge needle of 80 mm length (Sterican\textsuperscript{R}, B Braun, Melsungen, Germany), ensuring that no considerable amounts of the tracer were spilled. Based on the results of previous studies (Werner\textsuperscript{R}, Becton Dickinson, Madrid, Spain) was injected

| Location               | Clinically T-stage | Clinically N-stage | M-stage |
|------------------------|-------------------|-------------------|---------|
| Oropharynx (n=33)      |                   |                   |         |
| Soft palate (n=6)      | 1 x T1            | 6 x N0            | 6 x M0  |
| Base of the tongue (n=7)| 4 x T1            | 7 x N0            | 7 x M0  |
| Larynx (n=14)          |                   |                   |         |
| Supraglottis (n=6)     | 0 x T1            | 6 x N0            | 6 x M0  |
| Glottic (n=8)          | 0 x T1            | 8 x N0            | 8 x M0  |
| Hypopharynx (n=5)      |                   |                   |         |
| Piniform sinus (n=2)   | 1 x T1            | 2 x N0            | 2 x M0  |
| Retrocricoid (n=1)     | 0 x T1            | 1 x N0            | 1 x M0  |

n=number.

RESULTS

In all 50 patients one or more sentinel nodes could be detected intraoperatively. A total number of 90 sentinel nodes could be identified. Sixteen out of ninety sentinel nodes were found on the contralateral side in carcinomas, which were either situated in the midline or expanded over the midline (Table 2). Corresponding to the varying density of the lymphatics of the upper aerodigestive tract, the median number of identified hot nodes depended on the location of the primary tumour. When calculating median values it became evident, that carcinomas of the oropharynx and the supraglottis had two sentinel nodes, whereas glottic carcinomas usually had only one first draining lymph node.

During histopathologic examination a total of 2538 lymph nodes were analysed. On an average 36 lymph nodes (range 15–67) were examined histologically per neck dissection specimen (n=70).

Forty-one out of 50 patients had tumour free sentinel nodes reflecting the neck regional lymph node status (pN0), while in seven patients a solitary macrometastasis (H&E) and in one patient a micrometastasis (MNF 116) was proven during histopathological examination (pN1(mi)). In the remaining patient (T2 oropharyngeal carcinoma) a pitfall occurred (Table 3). The intraoperatively identified SN was shown to be tumour free during histopathological investigation. However, a directly neighbouring lymph node histologically proved to contain a metastasis of 0.65 cm in diameter with perinodal spread (pN1). This lymph node had not been suspicious on macroscopic examination. Intraoperative and extra-corpal readings of the dissected neck dissection specimen had shown no tracer accumulation within this lymph node. Thus there were nine patients with nodal disease and the procedure correctly identified eight of these (Table 4). Therefore, the sensitivity of sentinel node detection in this study was 89% or 89% (95% confidence interval 63–100%).
DISCUSSION

The controversy on the extent of surgical therapy of the clinically unsuspicous lymphatic drainage region of a malignant tumour occupies all surgical specialties. With regard to this background SN detection proved to be an accurate technique in melanoma (Ferwerda et al, 2000; Gennari et al, 2001; Veronesi et al, 2001). Corresponding to previously reported results in SN detection in easily accessible SCC of the upper aerodigestive tract like oral carcinoma (van den Brekel et al, 1999; Nieuwenhuis et al, 2000; Margolin et al, 2001; Zitsch et al, 2000), the SN concept may also be of significance in pharyngeal and laryngeal cancer, which so far have rarely been the topic of targeted investigations.

In contrast to the procedure in breast cancer we abstain from performing a preoperative dynamic lymphoscintigraphy as well as from additional injection of blue dye. In previous investigations (Werner et al, 1999) it could be shown, that transcutaneous readings in the area of the deep jugular lymph node level II – IV allow no exact identification of the sentinel nodes. Furthermore the depiction of lymphatic drainage in dynamic scintigraphy was tightly bound to the quality of the injection technique. Interferences through a poor exposure of the tumour, sudden movements of the patient or gabbage becoming evident and obscured the depiction of the lymphatic drainage into the representative main draining level of a primary tumour. Due to the fact, that intraoperative approach renders good exposure and precise injections because of the surgical field, but could also lead to delayed wound healing.

Table 2  Distribution of radiolabelled sentinel nodes

| Location                     | Unilateral neck dissection | Bilateral neck dissection | Total number sentinel nodes (SN) | Ipsilateral SN (n=) | Contralateral SN (n=) | Average of sentinel nodes (SN) |
|------------------------------|----------------------------|----------------------------|----------------------------------|---------------------|-----------------------|--------------------------------|
| Soft palate (n=6)            | 2                         | 4                         | 1 x one SN                       | 8                   | 4                     | 2                              |
| Tonsil (n=20)                | 12                        | 8                         | 5 x one SN                       | 36                  | 5                     | 2.05                           |
| Base of the tongue (n=7)     | 4                         | 3                         | 1 x one SN                       | 11                  | 2                     | 1.86                           |
| Supraglottis (n=6)           | 1                         | 5                         | 2 x one SN                       | 6                   | 4                     | 1.66                           |
| Glottic (n=8)                | 8                         | –                         | 6 x one SN                       | 10                  | –                     | 1.25                           |
| Piniform sinus (n=2)         | 1                         | 1                         | 1 x one SN                       | 2                   | 1                     | 1.5                            |
| Retrocricoid (n=1)           | 1                         | –                         | 1 x one SN                       | 1                   | –                     | –1                            |

No.: number; pts.: patients; ln.: lymph nodes; post N-status: histologically confirmed neck lymph node status.

In this clinically N0-neck patient group the rate of occult nodal disease was found to be 18%. The rate of micrometastases (<2 mm) with a size between 0.5 – 1 mm within the neck dissection specimen was 87.5% (7/8) in cases of histologically proven macrometastases within the sentinel nodes (n=8) and 0% (0/41) in cases of tumour free sentinel nodes (n=41). The number of isolated tumour cells was 21.9% (9/41) in cases of tumour free sentinel nodes (n=41). The number of isolated tumour cells was 21.9% (9/41) in cases of tumour free sentinel nodes (n=41). The number of isolated tumour cells was 21.9% (9/41) in cases of tumour free sentinel nodes (n=41). The number of isolated tumour cells was 21.9% (9/41) in cases of tumour free sentinel nodes (n=41). The number of isolated tumour cells was 21.9% (9/41) in cases of tumour free sentinel nodes (n=41).

Table 3  Results of sentinel lymphonodectomy in pharyngeal and laryngeal N0 cancer

| Location               | Histology of the sentinel nodes | Histology of the neck dissection specimen | Post N-status | Location |
|------------------------|---------------------------------|------------------------------------------|---------------|----------|
| Oropharynx             | 60 x tumour free                 | 1493 x tumour free                      | 27 x pN0      | 32/33 oropharynx |
|                        | 4 x macrometastasis             | 1 x macrometastasis                     | 5 x pN1 (mi)  | 14/14 larynx |
|                        | 1 x micrometastasis             |                                          | 1 x pN1       | 3/3 hypopharynx |
| Larynx                 | 18 x tumour free                 | 851 x tumour free                       | 12 x pN0      | 1/33 oropharynx |
|                        | 2 x macrometastasis             |                                          | 2 x pN1       |          |
|                        | 2 x pN0                          |                                          | 1 x pN1       |          |
| Hypopharynx            | 3 x tumour free                  | 104 x tumour free                        | 2 x pN0       |          |
|                        | 1 x micrometastasis             |                                          | 1 x pN1       |          |
|                        | 1 x pN1                          |                                          |              |          |

No.: number; pts.: patients; ln.: lymph nodes; post N-status: histologically confirmed neck lymph node status.

Table 4  Predictiveness of sentinel lymphonodectomy in pharyngeal and laryngeal N0 cancer

| Location               | No. of cases and % | Post N-status | Location |
|------------------------|--------------------|---------------|----------|
| SN predictive          | (49/50) 98%        | 41 x pN0      | 32/33 oropharynx |
|                        |                    | 7 x pN1       | 14/14 larynx |
| False-negative         | (1/50) 2%          | 1 x pN1 (mi)  | 3/3 hypopharynx |
| Sensitivity            | 8/9 or 89% (95% confidence interval 63 – 100%) |
The radioguided dissection of the 2–3 hottest nodes and the surrounding tissue may be a further step in reduction of radicality in surgery of the clinically staged N0 neck. However, the value of such an approach has to be examined in multicentric trials. As future perspective it may be possible to direct the efforts on a more limited surgical approach in this special indication.

Despite of the encouraging results we would like to point out, that perinodal spread may be a reason for non-accumulation of a tracer substance, which has been reported previously (Borgstein et al, 1998). The phenomenon of perinodal spread, which is usually seen in advanced metastatic spread, may also be evident in smaller metastases (Croce et al, 1992; Coatesworth and MacLennan, 2002), as could also be shown in one of our patients. The head and neck surgeon has to be aware of this fact, when performing and interpreting the results of SN detection in T3 glottic carcinomas. The limiting factor of the feasibility of this technique seems to be the reliable caudal margin of the tumour.

In conclusion it has to be assumed, that SN detection in carcinomas of the upper aerodigestive tract is first of all a diagnostic procedure. Through a targeted histopathological examination in serial sections the radio-labelled sentinel nodes may help to increase the diagnostic reliability of a limited neck dissection. This may help in decision making, whether more radical surgery is required, whether postoperative radio(chemo)therapy is necessary or whether a wait and see policy is justified.

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In summary, although we have shown, that skipping of nodal basin can occur, this technique still reliably identifies the sentinel nodes in pharyngeal and laryngeal cancer. Usually this applies to laryngeal and supraglottic T1-T2 carcinomas as well as T3 glottic carcinoma. The limiting factor of the feasibility of this technique seems to be the reliable caudal margin of the tumour.

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