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Sentinel Node for Accurate Diagnosis of the Head and Neck Carcinoma

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Abstract

When it comes to tumors of the head and neck, there is currently no reliable method for finding all the metastases of the neck. Therefore, we follow the rule of performing an elective dissection in the patients where more than 20% of metastases are expected. Even then, there are some patients with local recurrences. The explanation most likely lies in the incorrect histopathological diagnosis and unrecognized metastases. The ability to recognize smaller metastases can be accomplished by the use of the concept of the sentinel lymph node. This chapter describes the assessment of the neck status in 40 patients. In 18 patients, we have found metastases in the sentinel lymph nodes. It is important to note that in eight patients, metastases were found only after the use of serial cuts and immunohistological staining.

Keywords: sentinel node/s, serial section, selective neck dissection, head and neck cancer

1. Introduction

Metastases of the regional lymph nodes of the neck are the most important independent prognostic factor in the cancer of upper airways and upper digestive tract [1]. In the tumors of the same size, the presence of metastases of even one lymph node reduces the 5-year survival rate by 50% [2]. Despite the novel diagnostic methods, an accurate diagnosis of clinically nonsuspicious lymph nodes remains a big problem. There is currently no available method with which we could accurately find all the metastases of the regional lymph nodes. There are still a number of unsolved questions in regards to patients with a clinically negative neck. Thus, there is a dilemma of which investigative method gives us the most accurate results, do we need to treat a clinically negative neck, what is the optimal treatment, do we

need to treat the contralateral side of the neck, what are the chances of successful treatment of regional recurrences, and can we adjust the treatment to the etiology of the tumor [3].

Clinical examination with palpation is absolutely not sufficient for discovering small and occult metastases [4]. Newer methods such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) allow for a discovery of more occult metastases, but their use also results in a large number of false positive metastases [5]. With the use of CT and MRI, there is also a limitation of discovering the metastases of lymph nodes smaller than 5 mm [3]. The best results are achieved with the ultrasound investigation of the neck combined with a cytologic puncture [6]. Currently, no method is able to identify all of the occult metastases [7].

Therefore, we perform an elective dissection in the patients where more than 20% of occult metastases are expected [8–10]. Despite this, there remain a certain percentage of patients in whom the regional recurrences of the operated neck occur [11, 12]. Why is that? How can we overcome this? The most likely explanation is the unrecognized metastases in the dissected lymph nodes of the neck, overlooked by the classical histopathological examination. This oversight leads to inadequate treatment (no adjuvant radiotherapy) in these patients. An accurate neck status can be acquired by the use of the concept of the sentinel lymph node.

There is a large increase of patients with changed classification even with the use of only a classical histopathological examination. According to the literature, the classification increases in 49% and decreases in 21% [13]. With the use of classical histopathological examination, the pathologist examines the removed lymph nodes with one or two cuts along the longitudinal axis, which can lead to the oversight of the smaller metastases. With the use of the concept of sentinel lymph node, the lymph nodes are examined with serial cuts and immunochemical staining. This means that we can discover all of the metastases and can accurately determine the classification of the neck, which leads to the discovery of additional patients needing the adjuvant therapy. If elective dissection and checking for metastases of the lymph nodes are not performed, and we delay the adjuvant treatment until the possible appearance of metastases of the regional lymph nodes, the prognosis is worse [14].

2. The concept of the sentinel lymph node

The sentinel lymph node is the one which drains the lymph from the tumor first [15]. We assume that the tumor thrombus stops in the first lymph node that it reaches, and if there are no metastases in this lymph node, there will also be none in the other lymph nodes.

This concept is widely accepted in the surgical treatment of the malignant melanoma of the skin, as well as in the surgical treatment of breast cancer [16, 17]. In the treatment of the malignancies of the head and neck, there is a problem, which was highlighted by O'Brien [18], in the use of the concept of the sentinel lymph node due to the proximity of the tumor and the sentinel lymph node, rapid spread of the radiocolloid in the lymphatic pathways, a large number of the lymph nodes accumulating the radiocolloid, and often small, hard to reach lymph nodes.

Even though these difficulties referred to the skin melanomas, we encounter the same problems in the surgical treatment of squamous cell carcinoma of the upper airways and upper digestive tract. This is one of the main reasons why the use of the concept of the sentinel lymph node in the head and neck tumors is not widespread. The other important reason is that we do not have a fast and accurate method with which we could intraoperatively discover all of the metastases of the sentinel lymph nodes [19, 20]. A big problem arises if a pathologist discovers after the surgery the metastases in the lymph nodes that were not discovered with a frozen section procedure. In these cases, a reoperation is required, usually done 3–4 weeks after the initial surgery. Although we know that this can happen, it is still a very unpleasant experience for both the patient and the surgeon.

The examination of the sentinel lymph node with serial cuts and immunohistochemical staining allows for the discovery of even the smallest metastases [21]. It is important that if no metastases are found in the sentinel lymph node, there were also none in the other lymph nodes [22].

3. Selective dissection of the neck with the identification of the sentinel lymph node

In the cases where more than 20% of occult metastases are expected, we decide for the selective dissection, which means the removal of the lymphatics of the regions in which the metastases are expected [8–10]. In the oral cavity cancer and the oral pharynx, this depends on the localization of the tumor. In the tumors that are close to the midline, we must make a decision about the unilateral or bilateral removal of the lymph nodes. The decision can be made easier with the use of scintigraphy which can show us where the lymph from the region of the tumor drains. We remove the region of the neck which contains the sentinel lymph and additionally two adjoining regions. If the lymph is draining to both sides of the neck, we perform a bilateral selective dissection.

It has been proven that the survival of the patients in whom the elective dissection has been done is increased compared to the patients where the dissection was only done after the appearance of the metastases [14].

The patient disfiguring after an elective selective dissection is relatively minor when performed by an experienced surgeon. However, there is always a certain esthetic deformation larger than the one where only a sentinel lymph node is removed. There is also always a risk of damaging the marginal, accessory, lingual, and hypoglossal nerves. This nerve damage is rare in a careful surgical dissection.

After the removal of the lymphatics of the determined regions, we identify and remove the sentinel lymph node from the dissected material. The node is then examined by the pathologist with the serial slices at 100–150 microns and immunohistochemical staining. The remaining lymph nodes are examined with the classical histopathological methods with one or two slices along the longitudinal axis and staining with hematoxylin and eosin.

4. Preoperative identification of the sentinel lymph node

Preoperatively we determined the neck status of all the patients with the ultrasound. The study included the patients with T1 and T2 cancers of the oral cavity and oropharynx in whom no suspicious lymph nodes were found by ultrasound.

Approximately, an hour before the surgical procedure, a lymphoscintigraphy of the tumor region was performed. The static and dynamic scintigraphy allowed for the localization of the sentinel lymph node, which was marked on the skin.

5. Scintigraphy

For the determination of the sentinel lymph node, we used the Tc-nanocolloid. We used Nanocoll, produced by Amersham Health (Italy). Nanocoll is a set for the preparation of 99 m Tc-albumin nanocolloid. At least 95% of the parts of this colloid are equal or smaller than 80 nm.

We used 2–4 mCi, which correlates to 7,4–14,8 mBq. The amount of the radiocolloid used depended on the size of the tumor. Radiocolloid was injected at four different areas in close proximity to the tumor (above, below, left, and right; or clockwise—12, 3, 6, and 9 o'clock). By changing the needle positioning, we are able to infiltrate by colloid the entire tumor region. After the injection of the radiocolloid, the patient rinsed their mouth with water to remove any possible radiocolloid residues which might have influenced the investigation. 10 minutes after the application of the radiocolloid, we started to follow its movement along the lymphatics into the closest lymph nodes. For the detection of the radiocolloid, we used a gamma-ray camera Picker SX 300. Dynamic scintigraphy lasted between 45 and 60 min.

After an hour, we also made static recordings in the anteroposterior and lateral projections. Static scintigraphy allowed for the marking of the sentinel lymph node location on the overlying skin of the neck. If we were unable to identify the sentinel lymph node after an hour, we repeated the static recordings again in 30 min.

In this way, with the use of static and dynamic scintigraphy, we were able to identify the correct sentinel lymph nodes and limit any possible “skip” metastases [23].

6. Intraoperative identification of the sentinel lymph node

After we localized the sentinel lymph nodes with scintigraphy, we performed an elective selective dissection. After raising the subplatysmal skin flap, we injected the methylene blue dye to the same area where scintigraphy was performed before.

For the methylene blue dye, we used a Patent Blue V dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France). The amount injected depended on the size of the tumor (from 0.5 to 2 ml) since the entire area of the tumor had to be filled. We observed the spreading of the dye and

identified the sentinel lymph node as the one which colored blue. With the use of gamma-ray detector, we confirmed the accumulation of the radioisotope in the lymph node.

If the accumulation was 3-times larger than that of its surroundings, we considered it as a warm node, and therefore as our sentinel lymph node. Most of the sentinel lymph nodes turned blue and accumulated the radioisotope. However, there were some lymph nodes which only turned blue or only accumulated the radiocolloid, but not both. We treated these as the sentinel ones as well. We removed all the nodes that were assumed as the sentinel ones from the dissected material and sent them separately to a histopathological examination with the serial slicing. The rest of the lymph nodes were examined with the classic histopathological methods.

7. Examination of the sentinel lymph node and dissected material of the neck

The sentinel lymph node was prepared by the pathologist in paraffin blocks with serial cuts at 100–150 microns. With serial cuts, the alternating staining with hematoxylin and eosin and immunocytochemical staining with cytokeratin were used.

As a reagent for immunohistochemical staining, a reagent produced by Dako-Glostrup (monoclonal mouse anti-human cytokeratin clone AE 1/AE 3) was used.

All the remaining removed lymph nodes were examined with the classical methods of staining with hematoxylin and eosin in paraffin blocks with 1–3 slices along the longitudinal axis of the lymph node.

8. Results

Forty patients were treated with this method. In 18 out of 40 patients, we found metastases. In 10 of these 18 patients, the metastases were already discovered with the classical method (i.e., first cut of the sentinel lymph node). In 8 of the 18 patients with metastases, the metastases were only discovered after the serial slicing and immunocytochemical staining. In 3 of 10 patients in whom the metastases were already found with the classical method, the metastases were also found in the other lymph nodes, which meant that the N classification in these three patients changed from N0 to N2b. With the use of serial cuts of all sentinel lymph nodes, the classification changed from N0 to N2b in 4 of 7 patients.

9. Discussion

A final and accurate status of the neck provides us with a very good evaluation of the actual state of the neck and the need for eventual inclusion of the additional adjuvant radiotherapy. With the use of classical histopathological examination of removed lymph nodes after elective

dissection, we would have missed 8 out of 40 patients who did have metastases. Even with the use of only histopathological examination of the removed lymph nodes, we discovered 10 patients with metastases of the regional lymph nodes. With the use of classical method, the occult metastases were therefore discovered in 25% of the patients. This is an expected proportion of patients with the occult metastases [24–26]. To these patients, we have to add the patients in whom we have found the metastases with the serial cuts of the sentinel lymph nodes. There were eight of these patients. We see that the number of patients with occult metastases was close to 50%. With the use of classical histopathological examination, we would have discovered only around a half of the patients with the occult metastases. We cannot afford to examine all of the removed lymph nodes by serial cuts and immunohistochemical staining, due to the lack of personnel and funding. In selective dissection of the neck, we remove on average 13–15 lymph nodes, which would amount to more than 200 slices needing pathologist examination. Still, the question whether we would discover more patients with occult metastases remains. If we accept the concept of the sentinel lymph node [27, 28] that if there are no metastases in the sentinel lymph node that there are also no metastases in the other lymph nodes, the only question remains if the correct sentinel lymph node was selected. With the use of radiocolloid and concurrent intraoperative use of methylene blue, the identification is very reliable [29]. Even with the surgical method, when we remove only the sentinel lymph nodes, we discover many occult metastases with serial slices [30] that we otherwise would not have. This method has some weaknesses, mainly the possibility of missed metastases intraoperatively which are discovered afterwards [31] leading to an additional surgical procedure. Another potential problem is that we do not remove the true sentinel lymph node, which can happen due to a limited access and consequent inability to visualize the lymph flow by methylene blue. We may only see if the lymph node has stained or not, but we may not see if any other lymph node before has stained as well. In selective dissection where to gain access, we raise the entire subplatysmal skin flap, and we have a good visualization of the lymph drainage from the area surrounding the tumor. The visualization is also good when we use the gamma-ray detector to identify the lymph nodes which we marked on the skin when performing the scintigraphy. We often see many smaller lymph nodes on a very narrow area and if we would rely on the gamma-ray detector only, we could easily misidentify the sentinel lymph node. We can observe that after the removal of the sentinel lymph node, only the patients with regional recurrent disease have a very poor prognosis [32]. The possibility for recurrence is greatly increased if we have a larger number of metastatic sentinel lymph nodes. Micrometastases and isolated tumor cells do not have a larger influence on the possible recurrence [32]. The reason for this could be an overlooked true sentinel lymph node and the possible changes of lymph drainage and metastases found at unpredictable locations later on. With selective dissection where we remove the lymph nodes from the region of the sentinel lymph node's location and two adjoining regions, there is basically no chance to not remove all the lymph nodes with metastases, especially if adequate ultrasound or CT diagnostics were performed preoperatively.

Another question is if all of the metastases of the removed lymph nodes are found. If with serial slices and immunohistochemical staining in the sentinel lymph node we discover the metastases, there is also a possibility that the metastases are present in other lymph nodes. In 7 out of 18 patients, these metastases were discovered, even with the classical examination only. Therefore, there is a small chance that we have not discovered all of the micrometastases and

isolated tumor cells in the lymph nodes. If we assume that all of the lymph nodes containing these have been removed, we can conclude that they are not necessary for the further disease course. Micrometastases supposedly do not have an influence on the possibility of regional recurrences [32].

10. Conclusion

We can see that we do not have a method to preoperatively prove smaller metastases of the lymph nodes of the patients with the cancer of the upper airways and upper digestive tract. Even after a selective dissection with classical histopathological methods of removed lymph nodes, around 10% of the patients with metastases are missed. With a somewhat modified use of the concept of the sentinel lymph node, we can significantly decrease this number by discovering basically all of the metastases of the regional lymph nodes. A prospective study is needed to prove if the smaller metastases have an influence on the patient's survival and if they should be treated with additional adjuvant radiotherapy. However, there is an ethical question of not providing additional therapy to the patients with smaller metastases in numerous lymph nodes, despite the fact that they would not be receiving it with the classical examination of the removed lymph nodes anyway. There are also regional recurrences in the patients who have had a selective dissection, and the pathologist did not find the metastases in the removed lymph nodes. The percentage of these recurrences indicates that this might be these unrecognized metastases.

Conflict of interest

This study did not receive any external funding and was conducted during standard patient treatment. Therefore, there are no conflicts of interest.

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