Methylene Blue Staining Test in Early Detection of Head and Neck Cancers

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Head and neck cancers represent an important health problem in the present time. Due to the often late diagnosis and the significant changes that accompany the therapy associated with this disease, the impact on the quality of life of the patient is remarkable, causing a lower adherence to treatment, poor outcomes and an unfavorable prognosis. The current trend focuses on methods of investigation that allow an early diagnosis, which in turn translates into minimally invasive interventions with a favorable outcome. The purpose of this paper is to present the methylene blue staining method as an diagnosis tool, allowing the surgeon a better evaluation of the tumor and a more reliable limit of resection.

Keywords: methylene blue, head and neck cancer, early detection

Most malignant lesions of the head and neck area are squamous cell carcinomas [1,2]. The origin is represented by the squamous cells found on the surface of the upper aerodigestive tract. This includes the nose, oral cavity, throat and larynx. Although anatomically this areas are clearly separated, from a clinical point of view they have to be viewed as an unitary entity.

One of the main problems in the management of head and neck cancers is the late diagnosis [3]. If the disease is already locally advanced, the surgical intervention for the resection of the tumor will be more extensive, with a greater impact on the function of the organ, and the disease free status will be more difficult to obtain [4-7]. This is why the current trend focuses on the early diagnosis as a method of obtaining better results, with less impact on the quality of life of the patient, but most importantly with a higher overall survival rate.

A patient with a head and neck cancer will present with nonspecific symptoms [8]. These may vary according to the location of the tumor. The most common symptoms include nasal obstruction or a sinusitis that does not respond to treatment for the nose and sinuses, swallowing difficulties, foreign body sensation or a persistent sore throat when the pharynx is involved, hoarseness and breathing difficulties when the tumor is located in the larynx and swelling or persistent lesion for the oral cavity. All head and neck cancers may associate bleeding in the more advanced stages. Another important problem is represented by the so-called *unknown primary*, where the disease is diagnosed due to lymph nodes metastasis, but the primary tumor can not be located [9].

The risk factors most commonly present include tobacco and alcohol consumption [10-13], with a higher risk of developing the disease if both present [14-15]. These two risk factors can be incriminated in up to 75 per cent of all head and neck malignancies, especially for cancers of the oral cavity, pharynx and larynx [16]. Other risk factors include occupational exposure to asbestos, nickel or wood dust [17-18], infection with cancer-inducing types of human papilloma virus [19-21] or Epstein-Barr virus [22] and poor oral hygiene [23]. The main problem is represented by the high number of patients at risk due to smoking and alcohol consumption. A screening program for all these patients represents an important problem for all healthcare systems, due to the high financial burden.

The diagnosis is mainly based on visual examination of the suspected lesion. If at first the ENT surgeon had to rely on direct examination alone, the development of refined optical technologies allows us today a better assessment of the lesion and a correct diagnosis in earlier stages. The gold standard remains transnasal flexible endoscopy, using both white light and the Narrow Band Imaging (NBI) filter [24]. The investigations must be completed with imagistic examinations (computer tomography, MRI) in order to assess the real extension of the tumor [25-26]. However, the final diagnosis is established only by the histopathological exam of a biopsy sample.

The most important aspect in managing such patients is an early diagnosis. If a head and neck tumor is found in an early stage, the resection will be less extensive and with better results. Also, the impairment on the patient's everyday activities will be minimal. That is why our main focus is on finding new diagnostic tools, that permit an earlier and more accurate diagnosis. Another advantage of an enhanced optic tool is the fact that it allows us to evaluate the resection limit in-vivo.

Experimental part

The main purpose of this paper is to evaluate and present the benefits of the methylene blue staining test, taking into account the reliability of the method, for early stage head and neck cancers.

Methylene blue has important advantages when used on tissues, due to it's bacteriostatic and antioxidant properties, plus it helps the scaring process as well [27]. Also, unlike toluidine blue which is widely used for staining tests [28-31], it has less systemic side effects when swallowed. The use of the methylene blue staining method is acknowledged for laryngeal cancer, especially when combined with optical technologies such as videocontact endoscopy [32-33] or Narrow Band Imaging filter. We tried to determine if the same technique can provide valuable

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information when dealing with other head and neck cancers, such as the nasal cavity, pharynx or the oral cavity. The latest represents an area for which the lugol iodine staining test is accepted and extremely useful [34-35].

In order to asses the results of the method, we used the methylene blue staining test for patients with tumors of the nose, oral cavity and pharynx suspected to be malignant lesions. The test was performed prior to the surgical intervention, with the patients already under general anesthesia.

In all patients suspected of malignant lesions we first washed the tumor area with saline solution, then with 1% acetic acid. The area was dried, than colored with 1% methylene blue solution using a moist sponge. After an average waiting period of about 3 min, we cleaned the excess substance with 1% acetic acid.

The next step consisted in observing the staining pattern of the tumor area. We observed the pattern of dye retention, the shape of the tumor, the variations in color intensity, the aspect of the tumor's margins and compared them with the surrounding tissue. We found that the tumors have a dark blue intensity, compared to other light blue areas.

After the methylene blue staining test, we proceeded to the surgical intervention. Whenever possible, the entire tumor was removed with safety margins and sent for histopathological examination. Also, whenever suspect areas were revealed, we performed targeted biopsies.

Results and discussions

By means of observational study, we found that the methylene blue staining test allows a better evaluation of endocavitary head and neck cancers. The high intensity of staining is consistent with the tumor areas, indicating the most relevant places for performing biopsies.

A very important advantage of this method is the fact that we can evaluate the safety margins during the surgical intervention. If any tissue abnormality is revealed, we can simply extend the resection up to the limit where the tissue has a normal appearance.

We found that we can use the test for the assessment of suspicious lesions as well. The color pattern orients the surgeon in performing targeted biopsies. This is extremely important, because a quick diagnosis translates into less time before the therapy is initiated. Also, for early stage tumors, the benefits are important. In such cases, we may have difficulties in obtaining a diagnosis and any aid in performing the biopsy from the right area is extremely relevant.

However, the final diagnosis is established only by the histopathological findings. No adjuvant method alone can state for certainty that a patient has cancer, it can only orient the surgeon in performing the biopsies from the correct area.

Conclusions

We consider the methylene blue staining test to be a reliable and easy to use method. It can be performed for every patient, prior to the surgical intervention. The main advantage is that it orientates the surgeon in assessing the lesion.

Our observational study allowed us to state that the method can be used for tumors of the nose, oral cavity and pharynx as well, with good results. However, we consider further randomized studies are necessary for assessing the specificity and sensitivity of the method. Also, another development direction could be the use of the methylene blue staining test associated with refined optical technologies, such as video contact endoscopy or the use of Narrow Band Imaging filters.

The cost of the test is low, making it a potential screening method as well. It is easy to repeat, with no side effects for the patient.

Also, the experience of the surgeon plays an important role in the success of the method. Once he becomes familiarized with the method, it will be easy to use and practical, but it requires experience in assessing the data obtained.

The main advantages of the methylene blue staining test are the fact that it can be used for all endocavitary tumors of the head and neck, it is minimally invasive and easy to repeat and has reliable results. Head and neck malignant tumors are difficult to manage when discovered in advanced stages, due to the fact that an extensive resection can be difficult to perform and will affect in some degree the ability of the patient to perform everyday activities. An earlier diagnosis means a minimally invasive intervention with better outcomes. This why the methylene blue staining test is an important diagnostic tool in evaluating an early stage tumor or the tissue extension of a lesion.

The final diagnosis requires a histopathological examination of a sample biopsy. No staining method can replace the biopsy, it has only an adjuvant role. However, we consider it useful in assessing the lesion. Another development direction could be the use of this method as a screening method for patients at risk, but further research is necessary.

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