

ORIGINAL ARTICLE

Intraoperative localization of recurrences in thyroid cancer by ultrasound-guided injection of methylene blue

Localización intraoperatoria de las recurrencias en cáncer de tiroides mediante la inyección de azul de metileno guiada por ecografía

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Abstract

Introduction. The approach of a previously operated neck for metastasis resection faces a challenge to achieve a successful resection. The present study aims to demonstrate the usefulness of the ultrasound-guided injection of methylene blue technique for the intraoperative localization of recurrent lesions in thyroid cancer to facilitate their resection.

Methods. An observational, descriptive and retrospective study was conducted in patients reoperated for recurrences of differentiated thyroid carcinoma over a period of two and a half years, using ultrasound-guided intratumoral injection of methylene blue for its intraoperative identification. An analysis of demographic and clinical variables was carried out and its advantages over other methods were identified.

Results. This study included 10 procedures in nine patients, 77.8% women and 22.2% men, with a mean age of 54 years. All had a detectable and elevated thyroglobulin level before the intervention, 89% had a decrease in its level and 33% had an adequate biochemical response. The technique added 10 minutes to the surgical time. All marked lymph nodes were identified intraoperatively. The average number of lymph nodes resected was 12, of which six were positive, all with papillary thyroid carcinoma. It was considered of great utility and low cost in all cases.

Discussion. This technique is shown to be an effective strategy for the intraoperative identification of locoregional recurrences in thyroid carcinoma, allowing a successful lymph node dissection, reducing complications, surgical time and especially costs compared to other interventions.

Keywords: papillary thyroid cancer; local recurrence; lymph node excision; reoperation; methylene blue; ultrasonography.

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Resumen

Introducción. La cirugía para extirpación de metástasis en un cuello previamente intervenido afronta un reto para lograr una resección exitosa. El presente estudio pretende demostrar la utilidad de la técnica de inyección de azul de metileno, guiada por ecografía, para la localización intraoperatoria de lesiones recurrentes en cáncer de tiroides, para facilitar su resección.

Métodos. Se realizó un estudio observacional, descriptivo y retrospectivo, en pacientes reintervenidos por recurrencia de carcinoma diferenciado de tiroides, durante un periodo de dos años y medio. Se utilizó la inyección intratumoral de azul de metileno guiada por ecografía para su identificación intraoperatoria de recurrencia. Se hizo análisis de variables demográficas y clínicas.

Resultados. Este estudio incluyó 10 procedimientos en 9 pacientes, 77,8 % mujeres, con una media de edad de 54 años. Todos tenían un nivel de tiroglobulina detectable y elevado antes de la intervención; posteriormente, el 89 % presentó un descenso y el 33 % una adecuada respuesta bioquímica. La técnica agregó 10 minutos al tiempo quirúrgico. En el 100 % se identificaron de manera intraoperatoria los ganglios marcados; el promedio de ganglios resecados fue de 12, de los cuales, 6 fueron positivos, todos con carcinoma papilar de tiroides. Esta técnica se consideró de gran utilidad y de bajo costo en todos los casos.

Discusión. Esta técnica se muestra como una estrategia efectiva para la identificación intraoperatoria de las recurrencias locoregionales en carcinoma de tiroides, permitiendo una disección ganglionar exitosa, disminuyendo complicaciones, tiempo quirúrgico y, especialmente, costos frente a otras intervenciones.

Palabras clave: cáncer papilar tiroideo; recurrencia local; escisión del ganglio linfático; reoperación; azul de metileno; ultrasonografía.

Introduction

Thyroid carcinoma is considered the most frequent endocrine tumor, being more prevalent in the female gender, with a ratio of 4:1 compared to the male gender¹. Papillary carcinoma corresponds to the most frequent histological type, constituting around 85% of cases².

In general, differentiated thyroid cancer has a good prognosis, but locoregional recurrences have been found in up to 30% of cases, with involvement of the lateral compartment of the neck more than 50% of the time, while relapses in the central compartment are less than 30%^{3,4}.

Since the introduction of ultrasound as a routine method for patient follow-up, it has been possible to detect cervical lymph node recurrences less than 1 centimeter in diameter, which are generally not detected on palpation, since high-resolution ultrasound it can identify lesions from 2 to 3 mm in diameter^{5,6}.

When operating on a previously operated neck, it is important to bear in mind that there

will be some limitations in the surgical act, due to the distortion of the anatomical structures generated by fibrosis, local inflammatory processes, edema, tissue friability and obliteration of the tissues. Landmarks due to scar tissue, therefore, make it difficult to identify the lesion to be resected, reducing the probability of success of the procedure^{7,8,9}. In addition, it is important to highlight the increased risk of intraoperative complications, highlighting the recurrent laryngeal injury and parathyroid glands¹⁰.

In recent years it has been possible to implement a series of measures in order to reduce these difficulties. Among these, the role of intraoperative ultrasound to locate metastatic lesions stands out; however, the rate of failed resections has been found to be high^{11,12}.

As a strategy to increase surgical success in the removal of tumor relapses and to reduce the complications of surgery, the ROLL (radio-guided occult lesion localization) technique has been developed⁸, which consists of preoperative

intralesional injection, guided by images such as ultrasound or computed tomography, of a radiotracer, generally macroaggregated albumin labeled with Technetium-99, with which the concentration of the radiotracer in the target tissue is obtained and, intraoperatively using a portable gamma probe, detects the place with the most radioactivity and proceeds to resection¹³.

Another technique used is the intralesional injection of blue dyes, guided by ultrasound. In a study published by Sippel et al. at the University of California in 2009, they used three different blue dyes (lymphazurin, indigo carmine and methylene blue) for the location of suspicious lymphadenopathies, which due to their size could not be identified upon physical examination, in ten reoperations for recurrence of papillary thyroid carcinoma, showing the effectiveness and success in terms of resection of metastatic lesions in all patients¹⁴. Later, the same group published another study in a larger cohort, including 53 surgeries, in which it was confirmed that it was an effective and safe method¹⁵.

The objective of this study was to demonstrate the usefulness of the intralesional injection of methylene blue, guided by ultrasound, for the marking and resection of recurrent papillary thyroid carcinoma. With the implementation of this technique, it was sought to increase surgical success, as well as to reduce operative time and costs of the procedure.

Methods

A descriptive and retrospective study was carried out, in which individuals underwent reoperation for thyroid carcinoma were included, for the location of metastatic lesions in the neck with the intralesional injection technique of methylene blue under ultrasound guidance, between February 2018 and August 2020, by the Head and Neck Surgery service of the School of Health of the Universidad de Caldas, in Manizales, Colombia.

Ultrasonography, computed tomography, blood thyroglobulin levels, and fine needle aspiration cytology (BACAF) of the suspicious lesion were used to search for locoregional recurrence.

Patients with histologically proven recurrences were reoperated in at least one lymph node positive for metastasis.

In the operating room, with the patient previously anesthetized, ultrasound was performed by the head and neck surgeon with sufficient training and experience in ultrasound (Figure 1). The pathological lymph nodes were located and compared with the previous diagnostic images provided by the patient, verifying the adequate identification of the lesions to be intervened.

The pathological nodule was injected with 0.5 to 1 ml of methylene blue diluted in 5 to 10 ml of normal saline (0.9% SSN), under real-time ultrasound guidance (Figure 2). Staining worked effectively to stain the resected lymph node (Figure 3). After the extraction of the surgical specimen, it was sent to the pathology laboratory.

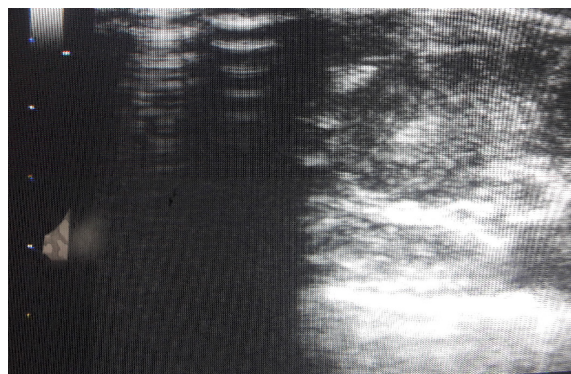


Figure 1. Sonographic location of the lymph node. Source: Doctor Andrés Ignacio Chala Galindo's file.



Figure 2. Intratumor injection of methylene blue under ultrasound guidance. Source: Doctor Andrés Ignacio Chala Galindo's file.

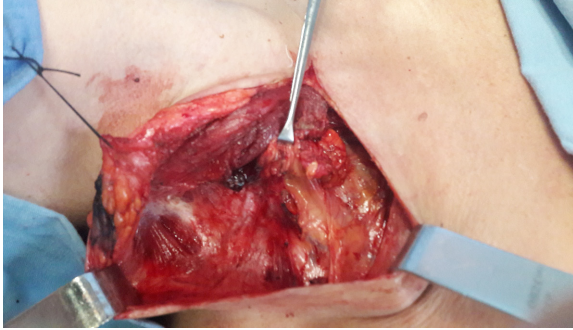


Figure 3. Intraoperative identification of the lymph node stained with methylene blue. Source: Doctor Andrés Ignacio Chala Galindo's file.

A review of the medical records of the identified patients was carried out and the data were entered in a database in Microsoft® Excel®. A descriptive analysis was carried out taking into account demographic variables, such as age and sex; clinical variables, such as thyroglobulin levels; imaging studies, before and after surgery, as well as fine needle aspiration biopsy cytology (BACAF), ultrasound and intraoperative identification of the suspicious lymph node stained with dye, the report of the pathology and the complications of the procedure.

Results

Between February 1, 2018 and August 31, 2020, ten surgeries were performed with this ultrasound-guided intratumoral injection technique of methylene blue, in nine patients with locoregional metastases, who had previously undergone total thyroidectomy. due to papillary thyroid carcinoma and central or lateral lymph node dissection of the neck, one of which was operated on twice in this period.

All patients were found to have papillary thyroid carcinoma. The ages of the patients ranged from 42 to 72 years, with an average of 54.1 years. The distribution by sex corresponded to 7 women (77.8%) and 2 men (22.2%). Regarding the location of the relapse, in two of the cases it was located in the central cervical compartment, seven in the lateral compartment, and one had a relapse in both compartments.

Relapse was identified in all of them by routine follow-up, with serum thyroglobulin levels, cervical ultrasound, and computed tomography; two of the cases had preoperative PET-SCAN. All patients had a detectable thyroglobulin level at baseline (mean 115 ng/ml). When the presence of suspicious lymphadenopathy was detected, it was confirmed by fine needle aspiration biopsy (BACAF).

In all cases, intraoperative identification and resection of the lymph nodes stained with the blue dye was possible. Localization was considered successful and highly useful by the surgeon in all cases. The average number of lymph nodes resected in each reoperation was 12 (range 1 to 47), of which an average of 6 nodes (range 1 to 26) were positive for papillary carcinoma metastases. In all of them, it was verified by the pathology report that the lymph node group identified in the surgical act was positive for malignancy.

Injection of methylene blue added approximately 10 minutes to surgical time in the operating room prior to the incision. There were no complications related to the injection of methylene blue. Difficulties during surgery were caused by the findings of scar fibrosis in previously operated patients, which was overcome with the identification of lymph nodes stained with methylene blue, to guide their resection. In no case were complications observed in the postoperative period, there was no resection of the parathyroid glands identified in the pathology report of the surgical specimens. Only one of the patients had intentional injury to the recurrent laryngeal nerve, due to the presence of a level VI paratracheal lymph node conglomerate, with invasion of the nerve, enveloped in 100% of the circumference; in this case, nerve resection was necessary and microsurgical reconstruction of the nerve was performed.

In the control imaging studies, it was found that the lesion was successfully excised in all cases, with a histopathological study that confirmed malignancy. During the follow-up period, in two patients (22.2%), locoregional lymph node relapse occurred, at different lymph node levels, which had not been previously identified, either by pre-surgical imaging studies, BACAF

or intraoperative findings. Of these, one of the patients underwent reoperation using the same ultrasound-guided marking technique, after which a successful removal of the tumor was obtained.

Thyroglobulin data at follow-up were available in nine of the cases. Preoperative thyroglobulin levels ranged from 0.2 to 300 ng/ml. Eight patients had a decrease in thyroglobulin after the surgical procedure. In three of the nine cases an adequate biochemical response was evidenced, defined as a thyroglobulin less than or equal to 2 ng/ml.

Reviewing the additional costs of the procedure, the value of the surgery when using this technique increased by an average of \$80,000 Colombian pesos, which corresponds to the cost of a soft tissue neck ultrasound, while, with the use of other techniques, such as ROLL, the additional value is approximately \$1,600,000 Colombian pesos.

Discussion

The incidence of thyroid carcinoma is increasing¹⁶. In the latest GLOBOCAN statistics¹, 567,000 cases were registered worldwide, ranking ninth in relation to other neoplasms, with a global incidence rate of 10.2 per 100,000 women, representing 5.1% of the estimated total cancer burden in the female gender. The mortality rate from this pathology is much lower than in other cancers, 0.4 and 0.5 deaths per 100,000 people in men and women, respectively, and with around 41,000 deaths per year.

In Colombia, according to data from the National Cancer Institute, for the year 2018, thyroid cancer in women ranked third, surpassed by breast and skin cancer, with a total of 512 cases, representing 11.1% of all cancers; while in men it ranked seventh, with a total of 114 cases and 3.5% of all cancers¹⁷.

Although it is true that differentiated thyroid cancer generally has a good prognosis, with a low mortality rate, recurrences have been identified in the neck, mainly metastases in regional lymph nodes, up to 30%³. Certain factors related to a higher risk of recurrence have been described, such as age less than 15 years or greater than or equal

to 55 years, male gender, follicular histology or a variety of tall cells, tack cells, tumor size greater than 4 cm, initial tumor local invasion and regional lymph node metastases¹⁸. In these cases, total thyroidectomy with central lymph node dissection is recommended, with unilateral or bilateral lymphadenectomy in whom regional metastatic disease is documented¹⁹.

In patients who have received iodine-131 therapy and who despite this persistence of lymph node disease is documented, surgical resection is indicated². Neck reoperation should be performed with caution, since difficulties during the intervention can result in a higher incidence of postoperative complications^{20,21}. Regarding the lesion of the recurrent laryngeal nerve and the parathyroid glands, reoperations of the central compartment and of the thyroid bed are more challenging for the surgeon, when compared with lateral neck dissections and primary thyroidectomy^{10,22}.

The other difficulty that arises during surgery on a previously operated neck is to be able to identify metastatic lesions, since, due to the small size of many of these, it is often difficult to differentiate them from scar tissue^{9,23}. For this reason, ultrasound has been implemented as a strategy to guide the surgical act, with the aim of facilitating the localization of the lymph nodes in recurrent thyroid carcinoma. McCoy et al. described the use of ultrasound in the preoperative marking of the lesion in patients with a single non-palpable lymph node, by marking the skin at the site where the suspicious nodule was identified by ultrasound and it was found that 100% of the patients had a satisfactory resection, while in patients undergoing cervical exploration without preoperative ultrasound marking the rate of negative examinations was 50%²⁴.

Preoperative planning, including ultrasound mapping, is essential to identify the location of the lymph nodes to be resected²⁵; however, with tissue incision and dissection, the preoperative orientation is often lost in the scar tissue, and although lymphadenectomy is possible, the index node can be missed, resulting in leads to unsuccessful resection attempts^{14,24}.

Although the role of intraoperative ultrasound is highlighted as a guide to localize resected recurrences, the number of failed resections is still high ²⁶, which is why the need has arisen to propose a series of strategies with the aim of overcoming these difficulties when dealing with recurrent thyroid cancer, impacting on greater surgical success and reducing complication rates ¹². These methods include preoperative ultrasound mapping ²⁵, intraoperative ultrasound ²³, ultrasound-guided needle localization ²⁶, guided dye injection ¹⁴, and radioguided surgery ⁸.

Radioguided surgery was initially described to locate non-palpable lesions suspected of malignancy in the sinus before surgery ^{27,28}. This procedure depends on the accumulation of a radiotracer in a target tissue, which facilitates its identification through the use of a portable intraoperative gamma probe ²⁹. Among the agents most used for thyroid and parathyroid reoperations are iodine-131, technetium-99, and technetium-99-sestamibi ³⁰. However, with the use of iodine-131 it is possible to achieve false positive results, such as when the radioisotope is captured by the thymus or submandibular glands, and false negatives, when the tumor foci are not detectable by the gamma probe ³¹. Efficacy by systemic administration of the radiotracer depends on the avidity that the tumor has for it, mainly in non-iodine avid papillary carcinoma ¹³.

The technique called ROLL is presented as an optimal alternative to overcome obstacles during reoperation ⁹. This method, which has become a standard for several breast units around the world ^{28,32}, has been extrapolated to individuals previously operated on for thyroid carcinoma, to facilitate resection of recurrent lesions with the help of a gamma scan portable probe, locating the site of greatest radioactivity ^{13,33}.

Recently, other strategies have been implemented, such as ultrasound-guided intralesional injection of blue dyes, but in Colombia no studies have been published with the application of this technique for the reoperation of patients with recurrent thyroid cancer. In our study we sought to demonstrate the usefulness of this me-

thod, with which the suspicious lesion could be identified by ultrasound and injected methylene blue, as a strategy that helps the surgeon to find abnormal lesions, with the aim of transforming a major surgery degree of difficulty in a simpler procedure, with better results in terms of resection of the recurrence and lower the rate of complications, taking into account that it is an intervention in patients who have previously undergone surgery ⁷⁻⁹.

We found several advantages of the intralesional methylene blue injection technique when compared to the conventional ROLL technique. Initially, it should be taken into account that not all institutions have access to the equipment and technology that a nuclear medicine service implies, and a high-cost portable gamma probe is a requirement for the intraoperative identification of lesions that capture the radiotracer. In addition, for the planning of the application of the ROLL technique, there must be coordination between the specialist in surgery and the specialist in nuclear medicine; whereas, in our study, the same surgeon was the one who performed the preoperative marking, and no additional personnel were required ³⁴.

Another important aspect to highlight is the time required for marking prior to surgery. If the ROLL is used, the radioisotope marking should be performed at least two hours before the intervention ^{3,4,13}, while in our study an average time of 10 minutes was estimated, the period in which it was performed ultrasound and injection of blue dye. This procedure was performed in the same operating room and with the patient previously anesthetized, which impacts on the decrease in pre-surgical marking time and on all the logistical coordination required by the nuclear medicine procedure.

The study had the limitation that a comparison could not be made in terms of surgical times, since there was no control group in which the technique was not used, but it is estimated that with the treatment of our patients the operative time was reduced by making the procedure technically easier.

In conclusion, this surgical technique is shown as a safe and effective strategy for the intraoperative identification of locoregional recurrences in patients with thyroid carcinoma, allowing a successful lymph node dissection guided by staining, reducing the risks of iatrogenesis, the time of the procedure and the costs of the intervention, since it is only required to have good ultrasound equipment and methylene blue staining, which is easily accessible and very low cost^{14,15}.

Compliance with ethical standards

Informed consent: This study is a retrospective medical record review, and as such, there is no need for informed consent. The Institutional Ethics Committee approved the design and methodology of the study.

Conflict of interest: The authors declare that they have no conflict of interest.

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Authors' contributions:

- Conception and design of the study: Ximena Franco-Castañeda, Andrés Ignacio Chala-Galindo.
- Data acquisition: Ximena Franco-Castañeda, Andrés Ignacio Chala-Galindo.
- Data analysis and interpretation: Ximena Franco-Castañeda, Andrés Ignacio Chala-Galindo.
- Drafting the manuscript: Ximena Franco-Castañeda, Andrés Ignacio Chala-Galindo.
- Critical review: Ximena Franco-Castañeda, Andrés Ignacio Chala-Galindo.

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