Lymphatic Mapping With Isosulfan Blue Dye in Squamous Cell Carcinoma of the Head and Neck

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Objective: To determine whether intraoperative lymphatic mapping with isosulfan blue dye and sentinel lymph node biopsy accurately demonstrates the pathway of regional metastases from mucosal sites in squamous cell carcinoma of the head and neck.

Design: A prospective clinical study of intraoperative lymphatic mapping.

Setting: An academic tertiary referral center.

Patients: Patients with previously untreated squamous cell carcinoma of the head and neck whose surgical treatment included neck dissection.

Intervention: Injection of isosulfan blue dye into the mucosa surrounding squamous cell carcinomas of the upper aerodigestive tract during cervical lymphadenectomy.

Outcome Measures: Correlation of the pathologic findings in the blue sentinel lymph node with those in the remaining cervical lymphatics.

Results: No blue-stained cervical lymphatics were identified after injection of the mucosa surrounding the primary squamous cell carcinoma with isosulfan dye.

Conclusion: The technique of intraoperative lymphatic mapping with isosulfan blue dye requires further study before it can be used for the detection of occult cervical metastases in squamous cell carcinoma of the head and neck.


One of the goals of head and neck surgeons treating squamous cell carcinoma of the head and neck (SCCHN) is the accurate identification of patients with clinically negative (N0) necks who harbor microscopic cervical metastases. Radiographic staging of the cervical lymphatics is imperfect because lymph nodes smaller than 1.0 cm are not considered suspicious by radiographic criteria yet may harbor metastatic disease. The most accurate method currently available for staging the N0 neck is pathologic examination of the neck contents after elective neck dissection. The identification of occult cervical metastases before neck dissection would represent an important advance in the treatment of patients with SCCHN. Since 60% to 70% of patients with N0 necks do not harbor occult regional metastases, preoperative diagnosis of microscopic metastases would identify the 30% to 40% of patients with N0 necks who would derive therapeutic benefit from neck dissection. Therefore, if there were a method to accurately identify occult metastases preoperatively, management of the N0 neck would be more selective and would reduce the overall morbidity and cost of treatment in cases that are now managed with the policy of elective neck dissection.

Patients with cutaneous melanoma now derive the benefits of a selective approach to the regional lymphatics through the technique of intraoperative lymphatic mapping with isosulfan blue dye and biopsy of the sentinel lymph node (SLN) as described by Morton et al. This technique is based on the concept that lymph node metastases from cutaneous sites follow an orderly progression from the primary site to the sentinel, or most proximal, lymph node. The technique, as it is used in extremity sites, involves injecting the perimeter of the cutaneous lesion with isosulfan blue dye (Figure 1). The blue-stained SLN is identified on visual inspection of the lymphatic basin, excised, and sent for frozen-section

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PATIENTS AND METHODS

ELIGIBILITY CRITERIA

Patients with SCCHN whose surgical treatment included neck dissection were eligible for entry into this study, which was approved by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, Pa. Patients with all sites and stages of SCCHN were included in the study. The original protocol stipulated that patients be staged N0, but was subsequently amended to include patients with clinical evidence of cervical metastases. The decision to amend the protocol to include patients with clinically palpable neck disease was based on our initial negative results in patients with N0 necks. Our thinking was that perhaps the lymphatic channels would be better delineated with the dye in patients with clinically positive necks. We are aware that the presence of metastatic cancer within the lymphatics may significantly alter the lymphatic drainage pattern and thought that this might actually help in visualizing the lymphatic channels.

The exclusion criteria were as follows: a history of neck dissection or radiotherapy to the head and neck, a previous reaction to dyes, a history of severe bronchial asthma, pregnancy, and age older than 18 years. Sixteen patients were entered into the study between January and August 1996. The Table gives the tumor sites and stages in these patients.

MATERIALS

Isosulfan blue dye is a Food and Drug Administration–approved substance that has been used for lymphatic mapping in humans. It is selectively absorbed into the lymphatics, bound to albumin, and excreted into the urine and bile. Rare allergic reactions to the dye are the only reported adverse effects.

EXPERIMENTAL PROTOCOL

Informed consent to participate in the study was obtained, and patients were taken to the operating room for their surgical procedure. After the induction of general anesthesia, 0.3 to 0.5 mL of isosulfan blue dye, in 0.1-mL aliquots, was injected into the mucosa surrounding the primary tumor. The skin flaps for neck dissection were elevated, and the neck contents were inspected in situ. We planned to mark the blue SLN with a suture if visualized. Selective neck dissections were performed for patients with N0 necks, and comprehensive procedures were performed for patients with clinical evidence of regional metastases. The neck dissection specimen was oriented and sent for permanent pathologic examination. The tumor was then excised and the surgical procedure completed.

EXPERIMENTAL OBJECTIVES

The objective of this study was to compare the pathologic findings in the blue-stained lymph nodes with those in the non–blue-stained lymph nodes to determine whether lymphatic mapping with isosulfan blue accurately identifies the pathway of the metastatic squamous cell carcinoma.

RESULTS

Sixteen patients with mucosal tumors of the upper aerodigestive tract were enrolled in the study. The tumors in the first 9 patients were staged N0, and no blue lymphatics were identified in any of these cases. The protocol was then amended to include patients with clinically positive lymph nodes in an attempt to identify any lymphatic structures with blue dye. No blue lymphatics were identified intraoperatively in the patients with clinically positive lymph nodes. There was confirmation that the dye was taken up systemically, rather than contained at the primary site, because the patients’ urine was noted to be yellow-green by the completion of the operation.

In summary, no blue lymphatic channels or cervical lymph nodes were visualized after injection of the mucosa surrounding the primary tumor with isosulfan blue dye. Sixteen cases involving mucosal tumors of the upper aerodigestive tract were studied with blue dye to assess the feasibility of mapping the pathway of the cervical lymphatics for mucosal sites of the head and neck. No blue dye was noted in any of the 16 patients with clinically negative or clinically positive cervical lymphatics. The study was terminated after we determined whether intraoperative lymphatic mapping with isosulfan blue dye and SLN biopsy accurately identifies occult metastatic disease in SCCHN.
that 16 was an adequate number of patients to confirm that our technique for lymphatic mapping as described was not an effective method of identifying the SLN.

COMMENT

Several technical difficulties were encountered throughout the study and are potential explanations for why isosulfan blue dye alone did not successfully demonstrate the cervical lymphatics draining primary squamous cell carcinomas of the upper aerodigestive tract in this study. The success of lymphatic mapping in melanoma rests in careful injection of the dye into the dermal, not the subdermal, lymphatics. Some authors report that injections of several milliliters of dye around the perimeter of the lesion are necessary to demonstrate the dermal lymphatics.10 In mucosal sites, the injected dye stained the primary site and surrounding mucosa intense blue and often made visual assessment of the gross tumor margin difficult. Attempts to inject more than 0.5 mL of the dye were limited by the tissue tension of the mucosa. The dye that could not be accommodated in the submucosal space spilled into the pharynx, causing intense staining of all the mucosa that it contacted.

The time course for transit from the injection site to the SLN is estimated to be 5 to 15 minutes for cutaneous melanoma, with lymph nodes losing their blue color after approximately 20 minutes.1 Skin flap elevation for neck dissection takes approximately 5 to 15 minutes, thereby causing the window of opportunity for visualizing the blue stained lymphatics to be missed. This technical problem was recognized after the first 2 patients with N0 necks were studied. Patients with oral cavity and oropharyngeal primary tumors were subsequently injected with the dye after the skin flaps had been elevated to account for the rapid transit time of the dye. Injection of laryngeal and hypopharyngeal sites required an injection apparatus and laryngoscope (Figure 2). Repositioning of the patient was required to place the laryngoscope and injection apparatus after elevation of the skin flaps. Injection of laryngeal and hypopharyngeal primary tumors may be impractical because of this technical point.

Another limitation specific to head and neck mucosal sites is the ambiguity of the lymphatic drainage patterns in the head and neck. Multiple and bilateral SLNs limit the use of isosulfan blue dye alone for lymphatic mapping in head and neck cutaneous melanoma.2 Unless lymphoscintigraphy is used to localize the SLN prior to biopsy, the skin flaps would need to be completely elevated for visualization of any of the potential SNLs in the neck. The SLNs in head and neck sites may be deep within the fascial layers of the neck and require more extensive and time-consuming dissection for visualization of the blue lymphatics. Biopsy of multiple and bilateral SLNs within the fascial compartments of the neck may be as time consuming as selective neck dissection and require the use of general anesthesia.

A learning curve of several cases is reported to be required to perfect the technique of lymphatic mapping in cutaneous melanoma. We did not identify any stained lymphatics after several modifications of our experimental protocol, which suggests that the nature of the mucosal lymphatics may be fundamentally different from that of the dermal lymphatics.

CONCLUSIONS

The technique of intraoperative lymphatic mapping with SLN biopsy will need significant refinements before it can be used to detect occult metastases in SCCHN. Further studies using blue dye and lymphoscintigraphy concurrently may demonstrate that intraoperative lymphatic mapping in head and neck mucosal sites is possible. However, even if the SLN is visualized with blue dye, technical considerations specific to head and neck mucosal sites may detract from its practical application in the cervical lymphatics. Until there is an accurate method to determine the presence of occult metastases before neck dissection, we recommend that neck dissection be performed electively for staging the N0 necks of patients with SCCHN.

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REFERENCES


