Intraoperative nerve monitoring in surgery for thyroid cancer

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Abstract: Surgery for thyroid cancer is multifaceted, especially as it relates to the management of the recurrent laryngeal nerve (RLN). Treatment of recurrent thyroid cancer may require reoperation and entail dissection through scar tissue and distorted anatomy. Intraoperative neuromonitoring (IONM) is a helpful tool in such cases and many other settings. Careful preoperative evaluation is imperative for assessing risk of RLN invasion and has important bearing on patient counseling and informed consent. Whereas anatomic identification of the RLN remains key, IONM adds a functional level of neural assessment. Understanding the dynamics of loss of signal (LOS) is important for determining surgical strategy, especially as it relates to staging of bilateral surgery and avoidance of bilateral vocal cord paralysis (VCP). Neuromonitoring information incorporated with knowledge of preoperative vocal cord function, patient-specific disease information, and surgical findings informs intraoperative decision-making as it relates to management of the invaded RLN. Additionally, IONM plays an important role in mapping and identification of RLN in the settings of revision surgery complicated by scar tissue and distorted anatomy. Optimized application of IONM requires knowledge of appropriate set-up and technique so that errors associated with equipment problems can be avoided. IONM guided decision-making allows a surgeon to optimize both functional and oncologic benefit.

Keywords: Surgery for thyroid cancer; intraoperative neuromonitoring (IONM); invaded nerve; loss of signal (LOS); staged surgery; vocal cord paralysis (VCP)

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Introduction

Surgical excision is the mainstay of treatment for thyroid malignancy. Surgery in the setting of thyroid malignancy involves careful management of the recurrent laryngeal nerve (RLN) and in cases of reoperation for recurrent cancers adds complexity of dissection through scar tissue and distorted anatomy. Intraoperative neuromonitoring (IONM) can have added benefit in navigating surgery for thyroid cancer.

The proximity of the RLNs to the thyroid gland places them at risk for involvement by tumor or inadvertent injury during surgery. When the RLN is invaded by thyroid cancer, surgical management is complex and requires robust perioperative planning and decision-making (1).

Loss of RLN function and resultant vocal cord paralysis (VCP) is a feared outcome of thyroid surgery. Unilateral VCP can present with mild to severe impairment, with symptoms including dysphonia, dysphagia, aspiration and dyspnea. Dysphonia is the most common presentation and can significantly impact quality of life, impairing one's ability to work or perform routine daily activities (2,3).

Moreover, severe emotional or psychological distress may be experienced as one adjusts to this condition (4). Bilateral VCP is an especially morbid outcome of thyroid surgery, with resultant airway compromise that may necessitate tracheostomy or acute airway intervention.

Rates of VCP after thyroid surgery are difficult to ascertain, as pre- and postoperative laryngeal examination is not uniformly performed and VCP may not be appreciated in some patients who are asymptomatic. Analysis of two large national databases (Scandinavian Quality Register and British Association of Endocrine and Thyroid Surgeons Audit) suggests that the detected rate of postoperative VCP doubles when postoperative laryngoscopy is routinely applied (5,6). Historically, the incidence of VCP after thyroid surgery has been reported as quite low, around 3–5%. However, it is likely that the true incidence is much higher. A recent systematic review of over 25,000 cases found the average rate of VCP to be nearly 10% (7) and a study of over 1,000 nerves at risk reported a 14% rate of temporary VCP for patients receiving thyroidectomy for differentiated thyroid cancer (DTC) (8). Bilateral VCP is fortunately a much rarer outcome, reported to occur in 0.1% to 1.3% of thyroidectomies (9-12).

While intraoperative visual identification of the RLN has long been recognized as important in preventing iatrogenic injury (13), visual identification of an intact nerve does not imply intact function. This is because a number of mechanisms of neural injury do not produce a visible alteration of the nerve. IONM offers a tool for dynamic assessment of neural function, which cannot be otherwise appreciated through visual inspection. Neuromonitoring information can be used to guide surgical decision-making, facilitating prevention of iatrogenic injury and informing the decision of whether to stage bilateral surgery in the event of injury. IONM data, when combined with clinical and patient-specific information, can also be used to guide surgical management of the invaded RLN. An additional important application of IONM in the setting of thyroid cancer is its role in mapping and identification of RLN, especially in the challenging setting of revision thyroid surgeries in recurrent thyroid cancers. The framework for optimized application of IONM will be reviewed herein.

Preoperative evaluation

Preoperative assessment of laryngeal function should be undertaken prior to thyroid surgery. At a minimum, preoperative voice assessment should be performed to establish a baseline (14). However, the sensitivity of voice abnormality in predicting the presence of VCP, ranging from 33% to 68%, is not optimal (15,16). In an effort to enhance voice outcomes in thyroid surgery, several medical and surgical societies have published best practice guidelines to standardize the performance of preoperative laryngeal examination. The American Head and Neck Society (AHNS), American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) and American Thyroid Association (ATA) have all recommended preoperative laryngeal examination for patients undergoing thyroid surgery who are at risk of RLN injury or involvement by tumor, including those with preoperative voice abnormality, a history of prior surgery placing the RLN or vagus nerve at risk, or malignancy with posterior extrathyroidal extension or bulky central neck adenopathy (14,17,18). The AHNS recommends flexible nasal endoscopy as the optimal method for evaluating laryngeal function and recommends preoperative laryngeal examination for all patients with thyroid malignancy (17,19). The German Association of Endocrine Surgeons recommends preoperative and postoperative laryngoscopy for all patients receiving thyroid surgery and the International Neural Monitoring Study Group (INMSG) recommends preoperative and postoperative laryngoscopy for all patients receiving neuromonitored thyroid surgery (20,21).

In the preoperative evaluation of thyroid cancer, the surgeon must maintain a high index of suspicion for involvement of the RLN by tumor. The RLN is a frequent site of invasion by locally aggressive thyroid cancer, with involvement occurring in 33–61% of cases of invasive DTC (22-24). Notably, invasion may be difficult to detect preoperatively, as up to 45% of invaded RLNs demonstrate normal vocal cord function (25). Therefore, careful preoperative risk assessment is imperative, even when preoperative laryngeal function is normal. Tumors which are large, located posteriorly, or show evidence of extrathyroidal spread should prompt concern for RLN invasion. Additionally, the presence of bulky central neck adenopathy or evidence of extranodal extension should alert the surgeon to the possibility of RLN invasion. Other clinicopathologic factors associated with invasive DTC include older age, aggressive histopathologic subtype (tall cell or sclerosing variants), and coexisting BRAF V600E and TERT mutations (26,27). When VCP is found to be present preoperatively, RLN invasion is likely to be encountered. Randolph and Kamani identified VCP in 70% of patients with invasive thyroid cancer *vs.* 0.3% in benign or noninvasive disease (15).

When invasive disease is suspected, preoperative cross-sectional imaging should be obtained to evaluate disease extent. The ATA recommends cross-sectional imaging, including axial computed tomography (CT) of the neck, be performed for DTC when there is a large primary tumor, bulky lymphadenopathy or clinical evidence of invasion (18). The AHNS suggests CT with fine cuts through the larynx and trachea be obtained when VCP is present and should be combined with endoscopy to evaluate for tracheal invasion and determine extent of surgery (19).

Assessing risk to the RLN(s) is imperative to counseling the patient about expected clinical outcomes and obtaining informed consent. It is important to have direct and detailed conversations with patients about anticipated intraoperative decisions and their impact on both oncologic outcome and voice and swallowing function. The decision of preserving *vs.* resecting an invaded but functioning nerve may be influenced by a patient's level of concern about risk of recurrence as well as their willingness to tolerate glottic dysfunction. This should be directly discussed with the patient so his or her preferences are known and can be incorporated into surgical strategy. Patients should be aware of the possibility that staging of bilateral surgery may be recommended based on intraoperative loss of neural function and their acceptance of this should be elicited preoperatively.

Overall disease characteristics, including histologic type, the presence of distant or unresectable locoregional disease, anticipated effectiveness of adjuvant therapy and patient preferences should impact intraoperative decision-making with regards to management of the RLN. The decision of whether to stage bilateral surgery after loss of RLN function on the initial side, for example, may differ based on the aggressiveness of the tumor and the urgency of completing thyroidectomy. Similarly, the decision of whether to resect all gross disease from an only-functioning nerve and risk bilateral VCP must be carefully considered. In each case, the decision-making should reflect an effort to balance oncologic benefit with functional outcomes.

IONM in thyroid surgery

Benefits and applications

The impact of IONM on rates of RLN paralysis is difficult to ascertain, in part because of the variable performance of preoperative and postoperative laryngeal examination for patients receiving thyroid surgery. Lack of standardization across studies with respect to surgical complexity and surgeon experience also limits the conclusions that can be drawn. Dralle *et al.* examined rates of RLN paralysis in a non-randomized multi-institutional prospective study of 29,998 nerves at risk and noted decreased rates of permanent VCP with use of IONM for low volume surgeons, though statistical significance was not met. Notably, reported rates of RLN paralysis are sufficiently low that a study adequately powered to detect a difference with IONM would be impractical; Dralle *et al.* calculated that such a study would require over 40,000 patients per arm for thyroid cancer surgery and over 9 million patients per arm for benign thyroid surgery (28). Meta-analyses have yielded conflicting results: Zheng *et al.* demonstrated decreased transient rates of VCP with use of IONM, whereas meta-analyses performed by Higgins *et al.* and Pisanu *et al.* found no impact of IONM VCP rates (29-31).

The benefit of IONM in high-risk surgical groups may be more readily demonstrated. Wong *et al.* conducted a meta-analysis and found decreased rates of overall RLN paralysis in reoperative cases and decreased rates of transient RLN paralysis in surgery for malignancy (32). In a retrospective study of 850 patients who received reoperative thyroid and parathyroid surgery, Barczyski *et al.* found decreased rates of transient RLN paralysis with use of IONM (33). A randomized study of 1,000 patients found a statistically significant lower rate of transient RLN paralysis in cases judged to be at high-risk of RLN injury, including those with anatomic branching patterns (34).

Despite the relative lack of high level evidence demonstrating improved outcomes with IONM, its benefits as a tool are recognized and supported by several medical and surgical organizations. The AAO-HNS guidelines for voice optimization in thyroid surgery acknowledge the benefits of IONM in neural identification and mapping, determining site and mechanism of injury, and prognostication of nerve function at the termination of surgery (14). The AHNS guidelines for management of invasive DTC suggest considering using IONM in all cases of thyroid cancer surgery, and the German Association of Endocrine Surgery and INMSG recommend routine use of IONM in all cases of thyroid and parathyroid surgery (19-21). The application of IONM has been shown to be feasible in a variety of surgical approaches, including minimally invasive and remote access thyroid surgery (35-37).

It should be noted that there is a small learning curve associated with IONM (38-40). If a surgeon intends to use

IONM for complicated and selected cases, he/she must be well versed with how to optimally use IONM, how to troubleshoot to avoid equipment related errors and how to correctly interpret IONM data. All of these are enhanced by routine use of IONM. Chiang et al have demonstrated that routine use of IONM reduced equipment-related problems from 4.4% to 0% (40).

INMSG has published comprehensive guidelines outlining the standard use of IONM (41,42). The major applications and benefits of IONM are as follows.

Intraoperative identification, mapping, and dissection of the RLN

The use of electrical neural mapping facilitates visual identification of the RLN. The nerve is mapped in the paratracheal region through electrical stimulation, with focused dissection leading to visual confirmation. Differentiating neural *vs.* nonneural structures through IONM permits identification of anatomic variants such as the anterior motor branch, which may not be recognized (38-40). IONM provides additional aid in mapping and identifying nerve in the setting of scar tissues and distorted anatomy frequently encountered in reoperation for recurrent thyroid cancer.

Intraoperative identification of impending neuropraxic injury

Evolving EMG changes observed during surgical manipulation can predict impending neuropraxia, allowing opportunity to cease injurious maneuvers and avoid severe neural injury (43,44).

Prognostication of neural function

At the termination of lobectomy, electrical stimulation can be used to determine the functional status of the RLN. This allows the surgeon to determine whether contralateral surgery should be staged in order to avoid bilateral VCP. Furthermore, if neuropraxic injury has occurred, retrograde stimulation along the course of the nerve can be used to identify the injured segment. This information illuminates the likely mechanism of injury, providing a learning opportunity for the surgeon and informing subsequent care.

Management of the invaded RLN

IONM data can be combined with surgical information and overall patient- and disease-characteristics to guide surgical management of the invaded RLN.

Set-up and technique

Application of IOMN requires an understanding of standard set-up and monitoring technique in order to prevent inaccuracies in data interpretation (21). The preferred method of IONM utilizes an endotracheal tube (ETT) with embedded surface electrodes that rest at the level of the glottis and record EMG activity of the bilateral vocalis muscles. Correct placement of the electrodes and avoidance of long-acting paralytics is essential to proper function and requires coordination with the Anesthesia provider. Correct ETT positioning can be assured by repeat laryngoscopy after patient positioning or by confirmation of adequate respiratory variation (45).

Intraoperative electrical stimulation of the vagus or RLN produces an EMG waveform with characteristic morphology, amplitude, and latency. A change characterized by a concordant amplitude decrease of >50% and latency increase of >10% suggests impending development of neuropraxia and should direct the surgeon to cease the associated maneuver (43). Importantly, reversal of adverse EMG changes occurs in 70–80% of cases if the surgical maneuver is modified within 40–60 seconds. With repeated adverse events, however, EMG changes become less reversible with increased risk of loss of signal (LOS), defined by the INMSG as an amplitude of <100 μV (42-44).

Inaccuracies in signal interpretation can be avoided by understanding and trouble shooting equipment-associated errors. Monitoring systems have stimulating and recording arms. Stimulating problems may result from inadequate stimulating current or failure of current conduction due to the presence of overlying tissue or blood, or the administration of a systemic paralytic agent, among others. Recording side problems include ETT malposition, loss of interface box and monitor connections, or pooling of saliva in the glottis (21).

As an initial surgical step, dissection and stimulation of the ipsilateral vagus nerve should be performed to confirm overall system function and avoid false negative responses (21). The INMSG recommends that a baseline response of >500 μV be obtained with a stimulation current of 1 to 2 mA, along with a detectable laryngeal twitch (42). If LOS occurs and a laryngeal twitch is present, a recording side error should be considered; ETT position should be assessed and electrical connections should be checked. If LOS occurs and laryngeal twitch is absent, a stimulating-side error should be considered. Stimulation in a dry field and testing the probe on muscle can confirm adequate stimulating current and absence of neuromuscular blocking agents. If a stimulating problem is not detected, stimulation of the contralateral vagus nerve should be performed. If the contralateral vagus response is present, an ipsilateral neural injury should be considered.

In order to maximize the predictive value of signal recovery, the INMSG has proposed that recovery be defined as a return of signal to >50% of initial baseline amplitude, with a minimum absolute value of 250 µV. This coincides with 50% of the recommended minimum response of 500 µV for initial vagal stimulation (42). Notably, if recovery occurs, it will typically be within 20 minutes (46,47). If LOS persists after waiting period of 20 minutes, staging of contralateral surgery should be considered to avoid risk of bilateral VCP (42).

Continuous IONM

Continuous IONM represents a newer format of monitoring which provides real-time uninterrupted RLN monitoring via placement of a temporary vagal electrode. The application involves automatic periodic stimulation (APS) of the vagus nerve and software-based assessment of EMG changes during surgery to monitor RLN integrity (48). A limitation of standard intermittent IONM is that injury may occur unnoticed between stimulations. The continuous IONM platform addresses this limitation, potentially allowing the surgeon to modify or abort an injurious maneuver before a significant adverse EMG event occurs (44). Anecdotal reports have raised concerns regarding cardiac complications as well as injury to the vagus nerve, either mechanically via circumferential dissection and application of the electrode or through repeated vagal stimulation (49,50). However, several studies have demonstrated no adverse events with use of this technique (43,44,51-53).

IONM and RLN injury

Intraoperative RLN injury may occur from a variety of mechanisms, including stretch, compression, thermal injury or transection. In a series of 281 injured RLNs, Dionigi *et al.* found traction injury was most common (71%), followed by thermal (17%), compression (4.2%), clamping (3.4%), ligature entrapment (1.6%), suction (1.4%) and transection (1.4%) (54). The majority of traction injuries occur at the Ligament of Berry, where dense fibrous tissue tethering the nerve can cause it to stretch with surgical manipulation of the thyroid (44,55,56). Importantly, traction injury may produce no visible evidence of damage, emphasizing the importance of neuromonitoring for functional assessment.

LOS may be classified as: type 1—a segmental injury with complete loss of response proximal to the injured segment but preservation of neural stimulation distal to it. Type 2 reflects a global-type injury where there is complete LOS along the entire course of the vagus and RLN without an identifiable point of injury. In a multi-institutional study, Schneider *et al.* prospectively examined 115 LOS cases and found traction to be the causative mechanism in 68% of type 1 injuries and 92% of type 2 injuries. LOS at the conclusion of surgery strongly correlated with postoperative VCP, with 82% of patients with persistent LOS demonstrating VCP on the first postoperative laryngoscopy. Rates of permanent VCP were higher in type 1 LOS, suggesting a more severe type of neural injury (55).

Persistent LOS at the conclusion of unilateral surgery should prompt the surgeon to consider staging of contralateral surgery to avoid bilateral VCP. The INMSG recommends that the surgeon acknowledge the morbidity of bilateral VCP and tracheotomy and prioritize this over concern about altering the original plan (42). Indeed, staged surgery after LOS has largely gained acceptance in the surgical community. Dralle *et al.* evaluated willingness to stage surgery after LOS in a survey distributed to over 1,200 surgical departments in Germany, with 94% of respondents indicating they would change their surgical plan in this setting (57).

The effectiveness of staged surgery in preventing bilateral VCP after LOS has been readily demonstrated, with several studies showing a zero percent rate of bilateral VCP if contralateral surgery is staged after LOS (55,58,59). Goretzki *et al.* reported that if surgery proceeded to the contralateral side with a known or unrecognized paresis on the first side, the risk of bilateral VCP was 17% (60). The high level of risk may be due to patient-related factors, including bilaterally symmetric high-risk anatomic variants. However, surgeon-related factors such as stress due to LOS on first side must be considered. Indeed, technical challenges related stress can lead to altered dexterity, rushed surgery, and impaired cognition and decision-making (61).

Salari *et al.* reported favorable oncological and neurological outcomes in 35 patients with advanced multi-compartment DTC or MTC who underwent planned staging of bilateral surgery (62).

A decision to proceed to the contralateral side after

LOS requires careful consideration in some cases. The mechanism of injury and the likelihood and expected timing of neural recovery should be assessed. Disease burden and aggressiveness as well as the urgency and necessity of complete thyroidectomy should be weighed. The patient's fitness for and willingness to undergo a second anesthesia should also be considered. Importantly, a preoperative dialogue with the patient and a multidisciplinary treatment team is important to streamline decision-making, facilitate informed consent, and manage patient expectations in surgery for thyroid cancer.

IONM and RLN invasion

Surgical management of the invaded RLN is complex and requires integration of multiple patient- and disease-related factors. The primary decision point involves whether the nerve should be preserved or resected. Importantly, the presence of RLN invasion neither independently influences survival (22), nor appears to impact prognosis (24,63-65). Rather, surgical strategy should be tailored to patient-specific disease and overall characteristics and should integrate this information with knowledge of preoperative vocal cord function, surgical findings and neuromonitoring data.

The degree of invasion can range from adherence to the nerve to complete encasement or infiltration by tumor. The ability to achieve macroscopic resection of tumor while preserving the nerve depends upon the extent of neural infiltration. When invasion is limited to the epineurium, shave excision with gross resection of disease is appropriate; while LOS may occur with this maneuver, neural function has been shown to recover majority of cases (64,66). On the other hand, when invasion extends into the perineurium or endoneurium with infiltration into neural fibers, gross total resection becomes difficult or impossible and the surgeon must determine whether resection is warranted.

Knowledge of preoperative vocal cord function is imperative for optimal decision-making with RLN invasion. When vocal cord function is intact and neural invasion is extensive, neural preservation should be considered within the context of several patient-and disease-related factors. For example, in primary treatment of DTC which expected to be radioactive iodine (RAI)-sensitive, leaving a small amount of macroscopic disease on an intact nerve may be appropriate. For aggressive cancers or disease for which adjuvant therapy is not expected to be effective, resection of the nerve may be warranted. The patient's age, disease characteristics, overall health status and preferences should figure into this decision. Older patients may not tolerate glottic dysfunction and aspiration and the surgeon may elect to leave a small amount of disease in favor of neural preservation. Some patients may favor more aggressive surgery in order to minimize risk of recurrence and need for additional surgery.

When preoperative VCP is present, neuromonitoring information informs the decision of whether to preserve or resect the RLN. Kamani *et al.* demonstrated that 33% of invaded nerves with preoperative glottic dysfunction still generate an EMG response when proximally stimulated (25). Resection of a nerve with intact proximal stimulability may therefore lead to loss of muscle tone and worsening of glottic function. Chi *et al.* demonstrated that preservation of invaded nerves with preoperative VCP but intraoperative proximal stimulability prevents development of vocal cord atrophy and decline of vocal function (67). The INMSG recommends that proximal stimulability as a parameter for decision-making in this setting (41).

Algorithms for management of the invaded RLN utilizing neuromonitoring information are published by the INMSG (41). These algorithms are based on preoperative vocal cord status and can be summarized as the following.

Invaded nerve with normal preoperative vocal cord function

When preoperative laryngoscopy is normal, extent of neural involvement guides the decision to preserve or resect, with shave resection being recommended for superficial involvement and patient- and disease-related factors guiding decision-making for more extensive involvement. To reduce the risk of bilateral VCP when neural resection is judged to be required, the INMSG recommends dissection be halted before LOS and surgery proceed to the contralateral side. If LOS occurs on the contralateral side, staged surgery may be offered to allow for neural recovery. If LOS does not occur or neural function recovers intraoperatively, resection of the invaded ipsilateral nerve can be safely undertaken.

Invaded nerve with preoperative ipsilateral VCP

When preoperative ipsilateral VCP is present, the INMSG recommends dissection of the contralateral side proceed first. This allows the full time of the surgery for an altered signal to return to normal. When function of the contralateral nerve is known to be preserved, testing of proximal stimulability for the ipsilateral invaded nerve facilitates the determination of whether to preserve or resect. In the absence of proximal stimulability, the invaded nerve is resected. If proximal stimulability is intact, patient- and disease-related factors described above influence the decision.

Invaded only-functioning nerve (contralateral VCP)

In cases where pre-existing contralateral VCP is present and surgery of an invaded but only-functioning nerve is undertaken, careful shave excision with adjuvant treatment is recommended. Resection followed by tracheotomy for bilateral VCP should be reserved for rare cases.

These algorithms provide a framework for surgical management of the invaded RLN and may be applied differentially for different disease types. While nerve preservation is generally favored, for more aggressive malignancies, the surgeon may have a lower threshold for nerve resection in order to facilitate complete resection (41). In each case, the balance of function and oncologic benefit should be tailored to the patient's specific disease and stated preferences.

Conclusions

Surgery for thyroid cancer is complex and involves special management of the RLN that requires careful preoperative assessment, surgical planning, and patient counseling. IONM enhances management of the RLN through intraoperative functional assessment, offering real-time dynamic guidance for intraoperative decision-making. Additionally, IONM provides important benefit as it relates to surgery for thyroid cancer by assisting in mapping and identification of RLN through scar tissue or distorted anatomy related to past surgery or extensive disease. Knowledge of IONM equipment functionality is important for avoiding pitfalls associated with equipment errors. IONM data along with patient and disease-specific information allows for a thoughtful and tailored approach to thyroid surgery.

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