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REVIEW

Anatomical variation in the right non-recurrent laryngeal nerve reported from studies using pre-operative arterial imaging

Anthony P. Polednak[1]

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Abstract

The right non-recurrent (inferior) laryngeal nerve (NRLN) is a rare anatomical variant associated with an arterial anomaly, the aberrant right subclavian artery (ARSA), that is detectable by pre-operative imaging (POI) using computed tomography and/or ultrasound. Most surgical studies have utilized two major types, NRLNs arising near the upper pole of the thyroid gland (type 1), vs. at a lower level (type 2) but with two subtypes defined by relationships to the inferior thyroid artery (ITA). This review found 8 English language surgical studies using POI that reported at least 1 NRLN and had anatomical information; of the 88 right NRLNs, 69.3% were classified as type 2 and 30.7% as type 1. Meta-analysis yielded a weighted proportion of 74.0% for type 2, but with substantial heterogeneity. For a subgroup of 5 POI studies with information on subtypes, 22 (59.5%) of 37 type 2 nerves were type 2a (i.e., running at or above the ITA). Similarly, a separate review of large surgical series without POI found that 60.4% of all 91 type 2 NRLNs were type 2a. The study findings should be relevant to the increasing numbers of anterior neck surgeries including bilateral thyroidectomies. A need was identified for studies on inter-observer reliability (agreement) among surgeons on NRLN types, and on injury rates (and related symptoms) by the type of NRLN.

Keywords Aberrant right subclavian artery · Anatomical variation · Meta-analysis · Non-recurrent laryngeal nerve · Recurrent laryngeal nerve · Thyroidectomy

Introduction

Surgeons have long recognized, at least since the early 1930s, the risk of iatrogenic injury to the rare right non-recurrent (inferior) laryngeal nerve (NRLN) [19], affecting the vocal cord function and quality of life. NRLNs were classified, based on earlier French literature, in 1988 [19] into 31 right NRLNs (0.6% of 4,921 right-sided surgeries) and 2 left NRLNs (0.04% of 4673 left-sided surgeries. One type arose from the vagus nerve at the upper pole of the thyroid gland (7 nerves) and another at a lower level (26 nerves) [19]. Avisse et al. [2] referred to these two categories as "type I" vs. "type II" or "transverse," running parallel to the inferior thyroid artery (ITA). Most widely used in the surgical literature is Toniato et al.'s [46] depiction of "type 1" and two subtypes of "type 2" described as either running "over" (depicted as above) the trunk of the ITA ("type 2A"), or under the ITA trunk or between its branches and ascending to the larynx ("type 2B"). Due to the variability among surgeons in the extent of searching for apparent recurrent (inferior) laryngeal nerves [20], NRLNs that are relatively easily (or inadvertently) detected may tend to be found, and anatomical variation in NRLNs may possibly be underestimated.

Iatrogenic injury rates have been reported as 13–14% for right NRLNs vs. 2–4% for RLNs in 2 large thyroidectomy series [38, 46]. The right NRLN, however, is associated with an aberrant right subclavian artery (ARSA). Pre-operative imaging (POI) using neck ultrasound (US) has been recommended to detect ARSA by the absence of the "Y sign" for the brachiocephalic artery [8, 10, 28]. Also, computed tomography (CT) scans detect the "hook-like" course of ARSA (usually retroesophageal), although angiography may be useful for confirmation [6]. These POI techniques can detect ARSA as a predictor of a right NRLN, although

The author has retired.

✉ Anthony P. Polednak
appoled7@yahoo.com

[1] Connecticut Tumor Registry, Connecticut Department of Public Health, Hartford, CT, USA

some studies focused on the prevalence (vs. on the anatomical features) of NRLN(s) found at surgery.

Anatomical variation in the origin and course of the NRLN may affect the risk of iatrogenic injury. A literature review was conducted to estimate the proportions of each of the three types of right NRLN (most often recognized in the surgical literature) [46], focusing on surgical studies using POI aimed at detecting ARSA as a predictor of a right NRLN.

Methods

Searches and eligibility criteria, and number of studies selected

Electronic searches (conducted in September 2018–January 2019) for "non-recurrent laryngeal nerve" produced: 97 items in PubMed; 2400 in Google Scholar; and 197 in Science Direct. Also, PubMed searches yielded 35 items for "ultrasound and non-recurrent laryngeal nerve" and 24 for "computed tomography and non-recurrent laryngeal nerve." A search for "laryngeal nerve and cadaver" produced 196 items in PubMed. Also, reviewed were all full-text English language cadaveric studies listed in a systematic review of recurrent (inferior) laryngeal nerve–ITA relationships [18]. Of 76 full-text articles of cadaveric studies reviewed, however, 26 studies (published as early as the 1930s and 1940s) reported a total of only 21 right NRLNs in 1070 right-sided dissections. Only one study mentioned the type 1 vs. type 2 typology [13], one used a different classification (without reference to the ITA) [28] and others had limited anatomical details. Therefore, the present review focused solely on POI surgical studies.

As recommended for systematic reviews, criteria for study eligibility were specified [34] as English language reports involving POI having information on the anatomical level of origin and/or course or type of a NRLN(s) and the total number of patients (i.e., case reports were not included). No limitations were made on the year of publication; however, POI with CT was first reported for predicting ARSA/NRLN in 1 patient in 2000 [32], and US (post-operatively only) for 12 patients in 2003 [10]. Of 52 full-text articles reviewed, 9 eligible POI studies were identified (Table 1), excluding the reports using a barium swallow test (for ARSA) [19, 46] usually limited to selected symptomatic patients (e.g., with dysphagia).

Statistical analysis

For unweighted proportions from multiple studies, 95% confidence intervals (CIs) were based on the binomial distribution, for small numerators. Unweighted prevalence, however, can be affected by an outlier(s) [3]. Meta-analysis provided a weighted pooled prevalence estimate (PPE) [17] of the proportion of NRLNs by type, and its 95% CI, using MetaXL software version 2.0 by EpiGear International Pty Ltd (Queensland, Australia). A random effects model was used with double arcsine transformation; back-transformation (normalization) yielded a sum of the prevalence for the two categories (absent vs. present) of 1 (i.e., 100%) [3]. Heterogeneity in prevalence of specific type(s) of NRLN among

Table 1 Non-recurrent laryngeal nerves (NRLNs) in surgical studies using pre-operative imaging (POI) with computed tomography (CT) and/or ultrasound (US) for arterial anomalies

Study, design, country, POI type	NRLN/total,[a] *n/n*	Level of origin; NRLN type as reported (in quotes) or as assigned in this review (in parentheses)
Huang [24], P, Taiwan, US	11/2330	1 at STA (1), 1 below ITA (2B); 9 above ITA trunk (2A)
Yetisir [52], P, Turkey, US	6/309	2 "type 1″, 3 "type 2a", 1 "type 2b"
Hong [22], R, So. Korea, CT[b]	15/2187	5 at STA "descending" (1); 3 "ascending" (2a); 4 "vertical" (2b) and 3 "V-shaped" (2b)
Lee [30], R, So. Korea, CT[c]	20/6546	2 "type I," 18 "type II"
Wang [49], R, China, CT[b]/US	5/1170	5 "type IIa"
Gong [15], P, China, CXR	23/1825	15 "type 1″, 2 "type 2a", 6 "type 2b"
Cai [6], P, China, CT[b]	4/783	1 at "upper pole of thyroid" (1), 3 at "mid-thyroid" (2)
Watanabe [50], P, Japan CT[b]	4/468	1 at STA "descending" (1), 2 at ITA "horizontal" (2), 1 "between" STA and ITA (2)
Total, 88: 27 type 1 (30.7%, CI 21.3–41.4%), 61 type 2 (69.3%, CI 58.6–78.7%)		
Type 2 subtype, 37: 22 type 2a (59.5%, CI 42.1–75.3), 15 type 2b (40.5%, CI 24.8–57.9%)		

CI confidence interval (95%), *CXR* chest x-ray, binomial distribution, *ITA* inferior thyroid artery, *P* prospective, *R* retrospective, *STA* superior thyroid artery

[a]Total surgeries with POI, right-sided, if specified

[b]All patients had CT of neck

[c]No data on total patients with POI

studies was assessed by the I^2 statistic (range 0–100%), with > 50% regarded as substantial [17].

Results

Surgical studies using POI

Of the nine POI studies with some anatomical information on right NRLNs, seven were from Asian countries, one from Turkey, and one from Italy. Five studies were prospective, apparently involving POI for all the patients in a defined time period, with at least some NRLNs predicted from POI of ARSA. Four were retrospective, assessing whether or not NRLNs that were recorded as found at the surgery could have been detected by the POI scans as reviewed by a radiologist or a surgeon trained in US. Not all ARSA, however, may have had a NRLN detected by routine surgical dissection [21]. A retrospective study in Italy using POI US [25] describing 17 NRLNs only as either "transverse" or "ascending" (i.e., possibly type 2) but without anatomical landmarks, was excluded from Table 1.

Table 1 shows data for a total of 88 right NRLNs from 8 studies. Total number of patients with POI (if available) for the right side (if reported) is also shown, although this is not a review of NRLN prevalence (i.e., only studies reporting at least one NRLN were eligible). Comments on individual studies focus on issues of study design, any NRLNs predicted prior to surgery, and problems using POI and/or NRLN typologies.

For POI with US, one prospective study reported detecting NRLNs using either 3.5 MHz or 10 MHz US; two false positives using 10 MHz were attributed to tortuous or short brachiocephalic arteries [24]. A prospective study mentioned "100% accuracy" for POI US, but without details [52].

For POI with CT, 1 retrospective study of 15 NRLNs reported problems defining type 2 subtypes, due to variability in the course of the ITA [22]; however, using the published schematic illustrations for each type, this review assigned a probable subtype (Table 1). For the 14 right NRLNs with CT scans reviewed, 5 had ARSA suspected pre-operatively [22]. A later report from the same institution covered two additional years of surgery, with no denominator [23]. Of the 11 patients listed (with data on age, sex, pathology, and NRLN type) [23], the present review identified only 1 case not previously reported [22] (not included in Table 1).

In a retrospective study of CT scans, 5 of 21 NRLNs had been suspected pre-operatively [30]. In contrast, a retrospective study using both CT and US reported that all five right NRLNs found during surgery were suspected pre-operatively from CT; retrospective review of US scans showed absence of the "Y sign" for all five [49].

In a prospective study in China using POI by chest radiology for all right-sided thyroid surgeries, 19 suspected ARSA cases were confirmed by CT; 4 additional NRLNs were detected by surgery alone [15], which is consistent with the low sensitivity of chest radiography for detecting ARSA [4]. The proportion for type 1 was high (hence, type 2 was low) [15] relative to other studies in Table 1 (Fig. 1). A retrospective study (not tabulated) using POI CT in China with 26 NRLNs had no anatomical data; notably, however, CT detected 25 ARSA, and angiography for 3 other patients found 1 additional ARSA [35]. Several reports mentioned invasiveness (radiation), cost, and delay in obtaining findings as drawbacks for routine use of CT.

For all 88 right NRLNs, the unweighted proportions were 30.7% type 1 and 69.3% type 2 (Table 1). For the 5 studies with information on subtype (60 NRLNs), the proportions were 23 (38.3%, CI 26.1–51.8%) type 1, 22 (36.7%, CI 24.6–50.1) type 2a, and 15 (25.0%, CI 14.7–37.9%) type 2b. Of the 37 type 2 NRLNs, 59.5% were type 2a, with CIs shown in Table 1.

Meta-analysis of POI studies

In a meta-analysis using the 8 POI studies, the weighted proportions (PPEs) were 26.1% (95% CI 10.7–44.9%) for type 1 and 74.0% (CI 55.1–89.3%) for type 2, with substantial heterogeneity (I^2 67.6%, CI 31.7–84.6%). This was influenced by the relatively low proportion for type 2 in one study [15]; the study weight is shown in Fig. 1. The PPE for type 2 was slightly higher than the unweighted proportion cited above and shown in Table 1.

For the 5 studies with subtype reported or assigned for 60 NRLNs, the PPEs were similar to the unweighted proportions shown in Table 1; that is, 36.6% (CI 4.2–72.8%), 38.4% (CI 5.1–74.3%) and 24.9% (CI 0.0–51.4%), with wide CIs. Heterogeneity was substantial ($I^2 = 85.0\%$, CI 62.8–94.0%).

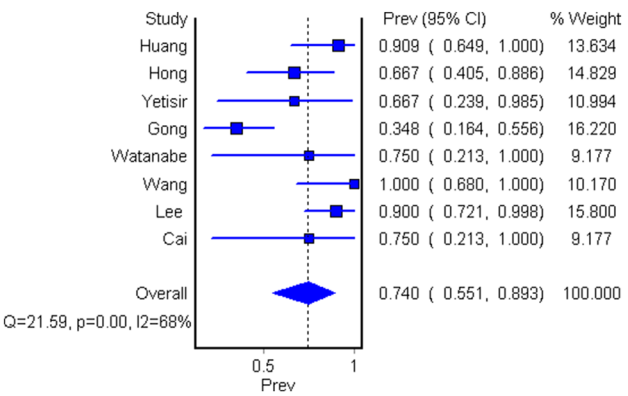

Fig. 1 Forest plot from meta-analysis of proportion of type 2 right NRLNs in eight studies

POI studies that also used intraoperative nerve monitoring (IONM)

Two retrospective studies using both POI CT and IONM that were reported from China had relatively high proportions for type 1 [14, 48], as also noted for another study from China using POI alone [15]. One of these two studies [48] reported 37 "type I" (50.7%), 33 "type IIA" (45.2%), and three "type IIB" (4.1%) of 73 right NRLNs. The other study [14] reported 8 "type 1" (88.9%) and 1 "type 2a" of 9 right NRLNs. In both the studies, the vagus nerve was monitored at two anatomical levels, as in other studies using IONM techniques that recognize the variation in the level of origin for NRLNs [14, 26, 48].

Discussion

In POI surgical studies, the type 2 NRLN predominated, but with substantial heterogeneity, including an apparent outlier from China (Fig. 1). For the subgroup of five POI studies with information on subtype for type 2 NRLNs, type 2a predominated, but also with substantial heterogeneity. In addition to statistical sampling variability, heterogeneity may reflect differences in study techniques [3] or real anatomical variability [17] reflected in geographic differences among countries in the proportion of a specific anatomical type of NRLN [48]. This review, however, found no reports with data on inter-observer reliability (agreement) among surgeons using the same typology, such as that of Toniato et al. [46], either within the same country or between countries.

Comparison with other surgical series

For comparison with the limited data on NRLN subtypes in POI studies, this review selected surgical series without POI (except for a barium swallow test for selected patients) that reported at least three NRLNs with some information on subtype (Table 2).

Henry et al.'s 1988 report [19] on 33 NRLNs (with 2 on the left side) included 7 arising at the upper thyroid level, vs. 12 related to ITA; the other 14 were presumably not type 1 but were not described in relation to the ITA. A study published in 1972 [42] included the drawings of right NRLNs arising at the ITA level vs. running above the ITA (type 2a in Table 2). From Italy, 1 study reported 14 of all 17 right NRLNs as "type 2A" [44] whereas another [46] described all 26 type 2 NRLNs as running under the ITA trunk or between its branches (hence, type 2b in Table 2). One study reported three patients each having two NRLNs arising from the vagus nerve at two different anatomical levels [9].

Of all 146 NRLNs, 19.9% were type 1 (Table 2), or lower than the figure in Table 1. Only one study, however, was from China [34] and one from another Asian country [29] vs. six from Europe or the USA (Table 2). Of all 91 type 2 NRLNs, 55 or 60.4% were classified as type 2a (Table 2); this is similar to the figure for the POI studies in Table 1.

Table 2 Non-recurrent laryngeal nerves: surgical series without pre-operative imaging[a]

Study, country	NRLN/total	Level of origin and/or type as reported (in quotes) or as assigned in this review (in parentheses)
Henry [19], France	33/4921[b]	7 at upper pole of thyroid (1); 4 "accompanying" the trunk of ITA (2a), 8 between ITA branches (2b); 14 others (2)
Stewart [42], USA	6/1776	4 upper thyroid/superior pole, "direct course"(1); 2 at ITA level, depicted as running at or above ITA (2a)
Defechereux [9]. Belgium	20/2517	2 upper thyroid pole (1), 13 above ITA (2a), 5 below ITA (2b). Included were 3 double NRLNs (2a and 2b)
Toniato [46], Italy	31/6000[c]	5 "type 1", 26 "type 2" included 20 under ITA trunk (2b), and 6 between ITA branches (2b)
Tartaglia [44], Italy	17/2713[c]	2 "type 1", 14 "type 2A", one "type 2B"
Page [36], France	3/887	3 "type I", no "type II"
Dolezel [11] Czech Rep	4/725	4 "type IIa", no "descending" or "ascending"
Qiao [38], China	28/6161	5 "type I", 19 "type IIa", 4 "type IIB"
Le [29], Vietnam	4 cases	1 "type 1″, 3 "type 2a." Total surgeries not reported
Total, 146 cases: 29 (19.9%, CI 13.7–27.3%) type 1 vs. 117 (80.1%, CI 72.7–86.3%) type 2		
Type 2, total 91: 55 (60.4%, CI 49.6–70.5%) type 2a vs. 36 (39.6%, CI 29.5–50.4%) type 2b		

CI confidence interval (95%), binomial distribution, *ITA* inferior thyroid artery

[a]Pre-operative imaging using a barium swallow test was reported for: 4 dysphagic patients [46]; post-operative for 20 NRLN [9]; and probably post-operative in another study [19]

[b]Includes two left NRLNs

[c]Total surgeries, right sides not reported

Study limitations

This review was limited to English-language reports. It was done independent of another review that was identified which focused on NRLN prevalence but without language restrictions [16]. Included were both surgical series (several finding no NRLN) and cadaveric studies, which accounted for only a small proportion of all 81 right NRLNs tabulated [16]. Aside from Henry et al.'s 1988 report [19], a large surgical series cited [16], involving 28 right NRLNs, was published in Chinese [51] but the English abstract indicated overlap with a study [15] included in Table 1. Also cited [16] was a publication in French with 15 NRLNs, but a later report in English (identified by the present review) did not use POI for 56 right NRLNs and had no anatomical information [37]. A publication cited [16] in Chinese with 12 NRLNs was updated later in English; POI was not mentioned and anatomical information was lacking for 15 NRLNs [40]. A report cited [16] in Japanese using POI CT [39], however, had 11 NRLNs not described in the English abstract.

This review (Table 1) included four POI surgical studies [15, 30, 49, 52] not in the other review [16]. Neither review, however, had a formal assessment of the quality of each study, which is considered to be part of evidence-based anatomy [45]; study quality also can be included as a variable in a meta-analysis [3].

Several studies were found that used IONM techniques that identified a NRLN(s), but did not mention POI and lacked anatomical information. The largest of these studies involved 25 right NRLNs in surgeries in Italy [1], and 11 right NRLNs in patients from both France and Italy [12]. Also excluded from Table 1 was a study of 1,710 right-sided thyroid–parathyroid surgeries in Poland using POI chest radiography and US; the 4 NRLNs were described only as running "perpendicularly" without the mention of anatomical landmarks [5], although this term could suggest type 1.

This was not a review of iatrogenic NRLN injury rates. Several studies, however, briefly mentioned no vocal cord palsies, NRLN "injuries" and/or "hoarseness" [2, 6, 15, 24, 42, 44, 50, 52]. Two studies using both IONM and POI reported no palsies [14] and no reduced vocal cord mobility at 1 day and at 6 months post-operatively [48]. No injuries were reported for 19 NRLNs predicted from POI chest radiography vs. 1 "incision" in 4 unpredicted nerves [15]. One "damaged" NRLN was "V-shaped" [22] (tabulated as type 2b in Table 1).

One injury occurred near the STA (type 1), however, despite POI findings in the medical record [30]. In a study without POI, three NRLNs were injured near the STA vs. one near the ITA [46]. NRLN type was not reported for three injuries [38], or for a temporary right-sided paresis [11]. Type 2 NRLN also has been described as presenting challenges for surgical identification [14, 15, 31]. Additional reports appear to be needed on injury rates by NRLN type, and negative voice outcomes after thyroid surgery may be detected using a combination of objective and subjective assessments [47].

Ultrasound of the neck/thorax has been recommended in many surgical studies as a non-invasive technique for pre-operative detection of ARSA, predicting a probable right NRLN and reducing the risk of NRLN injury; difficulties with patients with obesity and/or large goiter have been reported [8, 10, 25]. Issues with CT include invasiveness (i.e., radiation), cost, and delay in obtaining findings. IONM has been advocated for routine monitoring of laryngeal function, and for detecting right NRLNs to potentially reduce the injury rates [12, 26, 31]. For the related issue of RLN injuries, however, an extensive review found inconclusive evidence for IONM (vs. visual identification alone) in reducing RLN injury rates in thyroid surgery [7].

Other potential limitations involve difficulties in distinguishing the "ascending" or "vertical" type 2b NRLN (near the ITA) from a RLN with extralaryngeal branching [11]. This review did not address the anastomosis of the RLN with cervical sympathetic branches (the "false" NRLN) [10, 19, 24, 46], which reportedly may be detected by certain IONM techniques [12, 31]. Also, other types of NRLNs involve two separate branches ("bifid" NRLNs) originating at different anatomical levels [31], reported by Henry et al. (in 1988) for three cases (with a photograph of one) [19] and three patients in another report [9] (Table 2), along with a case report from Japan [27].

Conclusion

Future surgical studies should include an assessment of inter-observer reliability involved in using a specific NRLN typology. The present review, however, quantified anatomical variation in NRLNs from surgical series with and without POI (US and/or CT). Findings should be relevant to the increasing numbers of thyroidectomies (especially bilateral) for thyroid tumors [41] and also anterior cervical spine surgeries, for which both the RLN [43] and the rare right NRLN are also recognized as at risk of iatrogenic injury [33].

Author contributions APP: protocol/project development; data collection/management; data analysis; manuscript writing/editing.

Compliance with ethical standards

Conflict of interest The author has no conflict of interest with the present paper.

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