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Treatment of lateral neck papillary thyroid carcinoma recurrence after selective lateral neck dissection ☆

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ABSTRACT

Background: There is a paucity of data regarding optimal treatment options and outcomes for recurrent disease after lateral neck dissection in patients with papillary thyroid carcinoma.
Methods: Retrospective review of patients who underwent either percutaneous ethanol injection or surgery for first-time ipsilateral recurrences after ipsilateral lateral neck dissection for papillary thyroid carcinoma was performed.
Results: Follow-up data were available for 54 patients with recurrences in 57 lateral necks treated by either percutaneous ethanol injection ($n = 32$) or surgery ($n = 25$). Tumor burden at the time of lateral neck recurrence differed between the groups including the largest lymph node diameter (mean: 13 mm vs 18 mm, $P < .01$) and the mean number of metastatic lymph nodes identified on ultrasound (1.3 vs 1.9, $P = .04$). Each modality alone achieved similar estimated rates of disease control at 36 months (75% for percutaneous ethanol injection and 74% for surgery, $P = .8$) with similar number of reinterventions (1.8 for percutaneous ethanol injection, 1.6 for surgery, $P = .6$).
Conclusions: Both ethanol ablation and surgery can achieve disease control in the majority of patients with recurrences after ipsilateral lateral neck dissection for papillary thyroid carcinoma. Ethanol ablation, when used for treatment of a single small lymph node, can result in outcomes that are similar to reoperative surgery for larger and multiple lymph nodes.

Introduction

Lateral neck nodal metastases are relatively common among patients with papillary thyroid carcinoma (PTC), occurring in 12% to 81% of patients.[1] Reported ipsilateral recurrence rates after lateral neck dissection for PTC range from 8% to 26%.[2,3] Management of these recurrences can be challenging because neck reoperations can be technically difficult and there is potentially an increased incidence of perioperative complications.[4–9] Nonsurgical management options such as observation and the percutaneous techniques of radiofrequency ablation and percutaneous ethanol injection (PEI) have been described.[10–12] There may be a role for these options in a previously dissected lateral neck because of the technical difficulty and morbidity of reoperation or in patients who are high-risk surgical candidates. However, previous studies addressing recurrent thyroid cancer often encompass a heterogeneous patient population including patients with recurrences after previously performed lateral neck dissection (LND), lateral neck disease detected after the primary tumor has been treated but no lateral neck dissection has been performed, and central neck recurrences.[4–6,13–21] The aim of this study was to determine treatment outcomes of reoperation and PEI for the first-time recurrence within a previously dissected lateral neck. No prior studies have compared these two modalities directly.[11]

Methods

Patients who underwent selective lateral neck dissection for PTC metastatic to lateral neck lymph nodes (LNs) at Mayo Clinic, Rochester, Minnesota, were retrospectively identified. Medical records were reviewed for evidence of persistent or recurrent disease. All cases of persistent and recurrent disease were detected

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by ultrasound and confirmed with fine-needle aspiration cytology or thyroglobulin (Tg) needle washings. If multiple suspicious lymph nodes were detected on ultrasound, in some cases, only the most worrisome-appearing LN was biopsied. Treatment modalities included either reoperation or ultrasound (US)-guided percutaneous injection of the lymph node (PEI) using either 95% or 98% ethanol. The outcomes were analyzed according to the first treatment modality used for the first-time persistence or recurrence within the lateral neck previously treated by selective dissection. Follow-up consisted of at least one recorded outpatient visit with a comprehensive neck US performed, and the imaging and radiologic report were available for review. Every such visit was examined for evidence of suspicious lymphadenopathy. Patients without follow-up data available were excluded from further analysis.

Three LN diameters, volume estimate, and the presence of vascular flow in LNs were recorded for each LN treated by PEI on the initial pretreatment US and then on every subsequent follow-up US. Pre- and postprocedure unstimulated Tg levels were retrospectively identified on chart review. Absolute and relative change in Tg levels was calculated and compared between groups. Patients who had detectable antithyroglobulin antibodies were excluded from this part of analysis.

The outcomes of treatment were examined per lateral neck, and the main outcome of interest was disease control within treated lateral necks. At the individual LN level, PEI was considered to be successful if subsequent US findings revealed absence or nonvisualization of the treated lymph node, conversion of the treated lymph node to a normal US appearance, or volume reduction with no residual abnormal blood flow in the treated lymph node. The disease within particular lateral necks was considered to be controlled by PEI if successful treatment was accomplished at the individual LN and there were no other suspicious LNs on follow-up US. Disease control after reoperation was defined as the absence of suspicious lymphadenopathy on comprehensive neck US performed at our institution. Rerecurrence after PEI was defined as growth or reappearance of abnormal blood flow within previously treated LNs or detection of suspicious LNs outside of previously treated LNs. Rerecurrence after reoperation was defined as detection of any suspicious LNs within the lateral neck.

Statistical analysis was performed with JMP 13.0 (2016, SAS Institute Inc.). Time of rerecurrence after first reintervention was noted, and time from the first successful reintervention until first documented rerecurrence was used for Kaplan-Meier analysis of lateral neck rerecurrence after reintervention. Rerecurrence-free survival was compared between treatment modalities. The log rank test was used for analyzing survival time data. Discrete variables were reported as frequencies (percentage) and continuous variables as the mean ± SD. For analysis of categorical variables, either Pearson's χ^2 or Fisher's exact test was used. Differences between means were tested with one-way analysis of variance. A P value $< .05$ was used to determine statistical significance.

The study was approved by the Mayo Clinic institutional review board, and waiver of the requirement to obtain informed consent from the study subjects was approved considering the minimal risk of the study.

Results

Sixty-seven lateral necks (in 64 patients) were treated for first-time recurrences after 370 selective lateral neck dissections performed between 2000 and 2015. The recurrences were treated between January 2001 and June 2017. Follow-up data were available for 54 patients and 57 lateral necks (85%). Overall median follow-up was 57 ± 44 months (range: 8–177): 54 ± 48 months for PEI (range: 9–159), and 67 ± 45 in the surgical group (range: 8–177). Among patients with follow-up data available, average patient age at the time of recurrence was 52 ± 16 years (range: 22–92). There were 34 females and 20 males. PEI was the initial treatment strategy in 32 lateral necks (56%), and upfront surgery was performed in 25 lateral necks (44%). Tumor burden at the time of recurrence was different between lateral necks initially treated with PEI versus surgery, including the largest LN diameter (mean: 13 mm vs 18 mm, $P < .001$) and the mean number of metastatic LNs identified on US (1.3 vs 1.9, $P = .04$). Patients who underwent PEI were significantly older (average age PEI 58 ± 14 [range: 37–92] vs surgery 45 ± 15 [range: 22–78]). Radioactive iodine before recurrence was more commonly used in the surgical group (PEI $n = 23$ [72%] vs surgery $n = 24$ [96%], $P = .02$). Further details regarding characteristics of the primary tumors, recurrences, and prerecurrence treatments are summarized in Table 1.

Outcomes of PEI per individual treated LN

A total of 49 LNs in 37 lateral necks were treated by PEI. Follow-up data are available for 43 treated LNs in 32 lateral necks. The mean number of LNs treated per lateral neck was 1.3 (range: 1–3). A single LN was ablated in 21 lateral necks, 2 nodes in 8 lateral necks, and 3 nodes in 2 lateral necks. The average estimated LN volume was 257 ± 346 mm^3 (range: 27–1684 mm^3). The mean number of injection sessions per LN was 2 ± 1 (range: 1–8), with an average of 0.35 ± 0.27 mL of ethanol injected into a LN (range: 0.1–1.4 mL).

Overall, 20 LNs were not detectable on follow-up US, 16 had persistently decreased volume, and 7 LNs had increased volume after the initial response to PEI. As outlined in Table 2, significant differences were found between the initial dimensions of the LNs with different responses to treatment with PEI, including the average initial volume ($P = .04$), initial greatest diameter ($P < .01$), and initial smallest diameter ($P < .01$). Smaller lymph nodes were more likely to respond to PEI. The distributions of the LN dimensions are illustrated in Fig. 1.

Eighteen LNs were ≤10 mm in greatest diameter. In this group, 13 LNs were not detectable after PEI (72%), 4 (22%) had persistent volume decrease and 1 (6%) exhibited regrowth. Twenty-five LNs were >10 mm in greatest diameter, with treatment responses as follows: 7 were undetectable (28%), 12 had persistent volume decrease (48%) and 6 exhibited regrowth (24%) (Fig. 2).

Metastatic LNs that had initially responded to treatment by volume reduction started to increase in size at a median of 21 months after the last PEI session (range: 12–88 months). Overall, recurrences were detected in 9 lateral necks treated with PEI (28%); the majority of the recurrences occurred within previously treated LNs ($n = 6$; 67%). Recurrences in the remaining 3 cases occurred outside of a previously treated LN. The recurrences outside of previously treated LNs were detected after 12, 24, and 54 months.

Outcomes of reoperation

Reoperation consisted either of simple excision of nodal recurrence or redo dissection of at least one lateral neck level. Redo neck dissection was performed in 15 lateral necks, and simple excision of metastatic LNs was performed in 10 lateral necks. Excisions were more likely to be performed if the recurrence has occurred in a previously dissected lateral neck level (9 excisions, 90%) compared with 6 (40%) redo dissections that involved a previously dissected lateral neck level. Level II or level III dissections were most commonly performed ($n = 9$), followed by level V ($n = 6$) and IV ($n = 2$) dissections. The average number of LNs removed during reoperation was 7.1 ± 6.0 (range: 1–26), and the average number of metastatic nodes removed was 2.2 ± 1.8 (range: 1–8). Seven patients (28%) experienced persistence or recurrence after a redo surgery, and in 6 of 7 patients with persistence or recurrence

Table 1
Differences in tumor characteristics between treatment groups.

	PEI (n = 32)	*Surgery (n = 25)*	*Overall (n = 57)*	P
Initial tumor extent and treatment				
Primary tumor diameter, mm	22.2 ± 11.3 (8–50)*	26.6 ± 15.6 (7–75)	24.3 ± 13.6 (7–75)	.3
Extrathyroidal extension	18 (56%)†	13 (52%)	31 (54%)	.8
No. of LNs removed at initial lateral neck dissection	18.4 ± 7.1 (7–35)	19.7 ± 10.8 (8–61)	19 ± 9 (7–61)	.73
No. of metastatic nodes	3.9 ± 3.1 (1–13)	4.4 ± 1.9 (1–9)	4.2 ± 2.6 (1–13)	.17
Extranodal extension	5 (17%)	6 (24%)	11 (19%)	.43
Tumor characteristics at time of recurrence				
Time between first recurrence and initial lateral neck dissection, mo	22 ± 52 (2–168)	24 ± 35 (4–106)	24 ± 44 (2–168)	.79
Greatest diameter of recurrent LNs according to most recent pre-procedural US, mm	13 ± 4	18 ± 7	15 ± 6	<.01
No. of LNs involved by recurrence according to most recent pre-procedural US	1.3 ± 0.5	1.9 ± 1.6	1.6 ± 1.1	.04
Recurrence within previously dissected level of ipsilateral lateral neck	26 (81%)	15 (60%)	41 (71%)	.09

* Mean ± standard deviation (range).
† Number (%).*LN,* lymph node; *PEI,* percutaneous ethanol injection.

Table 2
Dimensions of lymph nodes treated with percutaneous ethanol injection, grouped by treatment response.

	Undetectable on follow-up (n = 20)	*Persistent volume decrease (n = 16)*	*Regrowth (n = 7)*	P
Volume, mm^3	153 ± 277 (27–1301)*	278 ± 269 (43–933)	528 ± 526 (124–1684)	.04
Initial greatest diameter, mm	9.6 ± 3.8 (5–20)	12.3 ± 3.2 (7–18)	14.9 ± 4.5 (10–22)	<.01
Initial smallest diameter, mm	5.1 ± 0.5 (3–13)	6.6 ± 0.6 (3–14)	8.4 ± 0.9 (6–13)	<.01

* Mean ± standard deviation (range).

(86%) simple excision was performed. Two patients (8%) have experienced postoperative complications, including one patient who developed Horner's syndrome and one patient who experienced a surgical site infection requiring wound debridement.

Comparison of outcomes "per lateral neck"—Surgery versus PEI

Overall, median follow-up was 57 months (53 months in PEI and 66 months in the surgery group, range: 8–177 months). Rerecurrence was detected in 9 lateral necks initially treated by PEI (28%) and 7 lateral necks initially treated by surgery (28%). There were no significant differences in lateral neck rerecurrence-free interval after reintervention between the groups (Fig. 2), with 75% of patients from the PEI group being free of rerecurrence compared with 74% of reoperated patients at 36 months ($P = .8$). The mean number of reinterventions was also comparable between groups (1.8 for PEI, 1.6 surgery, $P = .6$). Rerecurrence after PEI was treated by reablation in 5 lateral necks and by surgery in 4 lateral necks. Rerecurrences after surgery were treated by PEI in 3 lateral necks, and a second reoperation was performed in 2 lateral necks. Lateral neck disease control was not achieved in 2 lateral necks (in 2 different patients, who both had distant metastases and disease progression without documented attempts at lateral neck disease control).

Both pre- and postprocedural unstimulated Tg levels were available for 41 lateral necks without detectable anti-Tg antibodies. The average time between preprocedural Tg measurement and first reintervention was 1 ± 2 months (range: 0–7 months), and average time for postprocedure Tg level measurement was 5 ± 4 months (range: 1–25 months). The average preprocedure Tg level significantly differed between groups (PEI 4 ng/mL vs reoperative group 26 ng/mL, $P = .01$). There were no statistically significant differences in absolute Tg reduction (PEI 2.3 ng/mL, surgery 7.0 ng/mL, $P = .15$) or relative reduction in Tg serum levels between groups (31% PEI, 33% surgery, $P = .89$). Postprocedure Tg decreased to an undetectable level in one patient in each group.

Crossover between treatment modalities occurred at similar rates: 4 lateral necks initially treated with PEI (13%) subsequently underwent surgery; PEI was subsequently performed in 3 lateral necks initially treated by reoperation ($P = .92$). The difference in complication rates was not statistically significant (PEI, $n = 0$ vs surgery, $n = 2$ [8%]; $P = .1$). No perioperative or periprocedural mortalities were reported. The rate of distant metastases detected during follow-up was not statistically significant between treatment groups (PEI, $n = 6$ [19%] vs surgery, $n = 8$ [32%]; $P = .3$).

Discussion

The recent American Thyroid Association Surgical Affairs Committee Writing Task Force review stated that the use of PEI should be relegated to an alternative therapy category,[1] and the question of persistence of foci of viable tumor within nondisappearing LNs has been raised.[11] In this study, the majority of patients who underwent PEI had a durable response, either complete disappearance of the treated node or a long-term decrease in size. Our results are within the wide range of previously reported recurrence rates for PEI (3%–36%),[11] and this response was comparable to that of patients who underwent surgery for recurrence. Even though rare, late recurrences have been recorded within previously treated LNs, occurring in 19% of treated lateral necks and accounting for 67% of all recurrences when PEI is used.

Because PEI represents a form of berry picking, there is a concern for subsequent recurrences outside of the treated LN.[9] However, this recurrence pattern has occurred in only 9% of lateral neck recurrences treated with PEI and accounts for 33% of all recurrences in this group. It should be noted that most (86%) surgical recurrences occurred after simple excision rather than after redissection. Therefore, every effort should be made to determine the extent of prior surgery and determine if recurrence is within the previously undissected compartment and whether the patient may benefit from more comprehensive lymph node dissection. No specific cutoff can be derived from our data, but LNs >2 cm in largest diameter were generally not treated with PEI. The response to PEI was better in smaller lymph nodes, and no recurrences were detected in LNs with the greatest diameter <10 mm or LNs with the smallest diameter <6 mm. Taken together, these findings suggest that patients with larger metastatic lymph nodes, multiple lymph node involvement, and recurrence within a compartment that has not been previously dissected were selected for surgery rather than for PEI.

A theoretical concern has been previously raised regarding the potential of significant tissue fibrosis and sclerosis associated

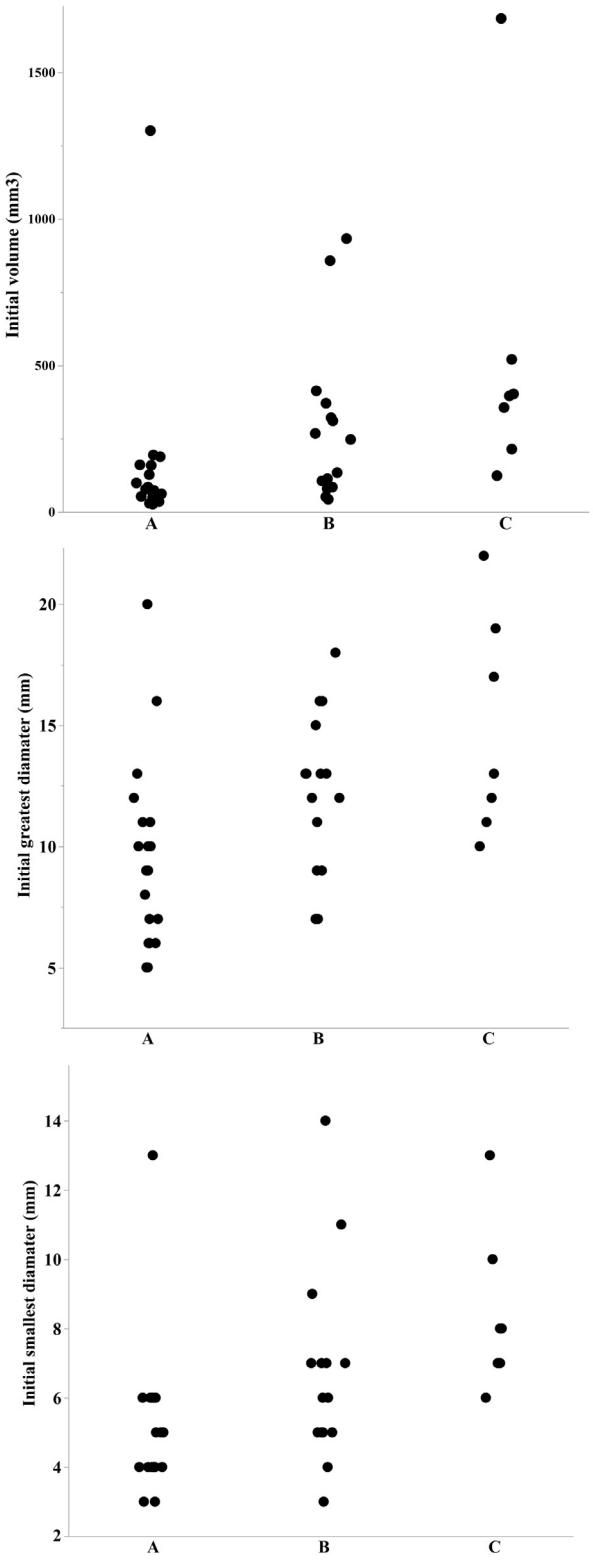

Fig. 1. Initial volume and greatest and smallest diameters of alcohol-ablated lymph nodes according to treatment response: (A) undetectable on follow-up; (B) persistent volume decrease; (C) regrowth.

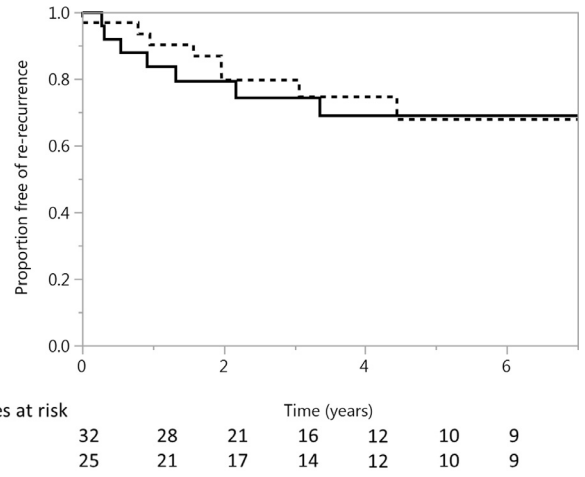

Fig. 2. Lateral neck rerecurrence free interval curves by treatment modality: PEI (*dashed line*) and surgery (*solid line*). *PEI*, percutaneous ethanol injection.

with ethanol extravasation, which would make subsequent surgery more difficult.[1] This question is difficult to study in our series because only 4 patients underwent surgery after the initial PEI. Furthermore, it is difficult to quantify and study retrospectively, and a surgeon may not be able to discern fibrosis caused by a prior operation from the fibrosis induced by ethanol. However, no complications have occurred after reoperation in this very limited group of patients.

Prior reports of reoperations for locally recurrent PTC include a wide range of both recurrence rates (0–29%) and complication rates (1%–33%).[11] Only 2 studies have separately described the scenario addressed in our study,[3,22] and both studies describe low long-term recurrence rates after reoperations within previously operated necks (2%–3%). However, outcomes of reoperation were not the focus of either of the studies, and there may be differences in methodology because we used the Kaplan-Meier method. Chereau et al[3] reported a complication rate of 8% in a setting similar to that in our study, which found a 7% rate of complications. Higher complication rates generally associated with reoperation for recurrent PTC may be due to inclusion of central neck reoperations in prior series and associated recurrent laryngeal nerve injury risk, as well as hypoparathyroidism, and therefore may not be applicable to lateral neck dissection.

Finally, it should be noted that our study spans a relatively long period (16.5 years), and the approach to locoregional recurrences of PTC has changed during this time. It was recognized that local recurrence of PTC, even if progressive, may have a relatively indolent nature, and recent studies have suggested that observation may be a safe strategy.[1,10] Specifically, current guidelines from the American Thyroid Association suggest that LNs <10 mm can be observed, and some of the recurrent LNs reported in our series were below or close to this cutoff.[9] It should also be noted that response to treatment was measured in purely structural terms and that the biochemical response was variable.

This study is limited by its retrospective single-institution design. There were significant differences in the extent of disease between two treatment groups, and therefore, relative performance of two treatment modalities should be compared and interpreted with caution. Selection bias, small numbers of patients, and associated low power preclude us from making strong recommendations regarding possible criteria for selection of appropriate candidates for PEI.

Conclusion

Lateral neck recurrence after selective neck dissection for papillary thyroid carcinoma may be difficult to control. Both ethanol ablation and surgery can achieve disease control in the majority of patients. Ethanol ablation, when used for treatment of single small

lymph nodes, can result in outcomes that are similar to those of reoperative surgery for larger and multiple lymph nodes.

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Discussion

Dr Jack Monchik (Providence, RI): Very nice paper, and this is a very difficult problem. I suggest that what you have shown here is that for the larger nodes, alcohol ablation was not as successful. Previously we showed that in the lateral neck, radiofrequency ablation for nodes that are 2 cm or larger was more successful. I suggest that you think about radiofrequency ablation for these nodes in the future. You can't use radiofrequency ablation in the central compartment because of the recurrent laryngeal nerve, but in the lateral compartment, it's an option as long as it's not near a nerve.

Dr Veljko Strajina: Thank you.

Dr Cortney Lee (Lexington, KY): I do use alcohol ablation on specific patients that really aren't great surgical candidates for recurrent disease.

You said that you can't really compare things but it looks like the tumors were larger, the nodes were larger, the disease was a little more aggressive, et cetera. So you suggested equivalent outcomes, but the surgery group had worse disease to begin with. What do you speculate would have happened if this entire cohort was treated with alcohol ablation?

So if the take-home message is that they are equivalent, but when we look at the disease to begin with, perhaps you were just treating different diseases.

Dr Veljko Strajina: This is an excellent point, and there is not much to add. However, it is unlikely that many of these patients will ever get alcohol ablation.

Dr Paul Graham (Houston, TX): What were your contraindications to alcohol ablation? And then how many patients crossed over, maybe had a reoperative lateral neck dissection and then had alcohol ablation? Maybe they had limitations of one treatment modality then finally changed to a different modality.

Dr Veljko Strajina: Patients were grouped according to the very first modality used to treat the recurrence.

And then subsequently (this would be treatment number 3), the cross-over rate was about 12% in both groups. Alcohol failed in certain patients, and 12% of patients initially ablated had surgery. A similar rate is seen in the group of patients initially treated surgically.

Dr Herb Chen (Birmingham, AL): You alluded to the fact that a lot of patients may have been observed, and that's important because usually when we are thinking about a re-intervention, our threshold to intervene is much higher.

How many patients do you think recurred after initial surgery that did not have any intervention? And then second of all, it would be important to compare that group with these two groups with regard to survival. What would you expect the survival differences to be in patients who are observed or ablated or have reoperative surgery?

Dr Veljko Strajina: We can only speculate, since there is no observation-only group.

Regarding the effects on survival in this very small group, and survival effects of treating recurrent disease in general, these patients likely do not die of lateral neck disease. About 30% of these patients have distant disease. Therefore, it appears that another recurrence after lateral neck dissection suggests more aggressive disease. That is where the mortality comes from, most likely. Therefore, I would guess that it would be difficult to demonstrate any

survival advantage from a single modality used to treat lateral neck recurrence.

Dr Ashok R. Shaha (New York, NY): You use the phrase *compartment-oriented dissection* in the title. Just for my knowledge, can you define what you mean at Mayo Clinic by that terminology, *compartment-oriented dissection?*

We have a large number of patients at Memorial just followed for a long period without operation. We intervene only when there is a demonstrable increase in disease or a concern about the location. In your patients, how did you make the decision that this patient should undergo an ablation? Was it your decision? Was it the patient's decision? Was it the surgeon's decision when they didn't want to operate on that patient?

Dr Veljko Strajina: That is an excellent question.

I do not think that I can give you a data-based answer. It is a combination of many factors. Some patients come from elsewhere and specifically want alcohol ablation. Sometimes it was a decision between the endocrinologist and the patient. Sometimes surgeons were involved. But I do not think that we can define a protocol or specific criteria for how to select these patients other than in the general terms that you can see in the Conclusion. With smaller nodes and less disease, we are considering alcohol ablation.

And I think that *selective neck dissection* is the appropriate terminology.

Dr Ashok R. Shaha (New York, NY): You use the words *compartment-oriented neck dissection*, so I'm just curious about that terminology. I know it started at M. D. Anderson many years back, but I just wanted to get your definition of the terminology.

Dr Veljko Strajina: Thinking about the terminology that should be used, *selective neck dissection* is the appropriate term.

Dr Mark Cohen (Ann Arbor, MI): If you are involved in making a decision about how you are going to impact patients with this in terms of disease control, how is this going to have any long-term impact?

As I looked at your data, one of the questions that came up was if you are comparing thyroglobulin response after intervention. You said there was some response in both groups but it wasn't really statistically significant. Did you actually separate out those that had a full neck dissection versus plucking out a couple of nodes?

Dr Veljko Strajina: Do you mean at reoperation or the initial operation? At the initial operation, they all had formal neck dissection. With reoperation, you likely achieve some control but you rarely eradicate the disease. If you attempt to identify the patients who had a complete biochemical response and undetectable thyroglobulin after these re-interventions, there was 1 patient in each group. So, 1in 30 patients would have undetectable thyroglobulin after intervention, suggesting that there is disease elsewhere for the others.

Dr Fiemu Nwariaku (Dallas, TX): I applaud you for your presentation and for taking these questions. I would like to push you a little bit. Your study has two separate groups of patients. As you said, these are two different groups. So comparing them is a little bit unfair to both of them.

I wonder if you take out the group who had large bulky tumors, and you just analyze the people who had small local disease, and compared ethanol versus, say, a simple outpatient operation to take out those lymph nodes, what would be the outcome? Because if you look at the data, the survival is similar, recurrence is similar, and so really you are looking at lowering thyroglobulin levels and other soft endpoints. Did you do that kind of analysis? If you did, what would you expect to find?

Dr Veljko Strajina: I wish we were able to do that, to match these 2 groups and then compare the outcomes. I would suspect that surgery would probably be better, but I really cannot answer that question. This is a very small group of patients, and our ability to match these two groups is limited. But such a study would give us better answers.

Dr Jennifer Kuo (New York, NY): I have two questions. First, could you elaborate on your protocol for the ethanol ablation? Was it a single ablation, and then that was the starting point of your analysis? Or did you bring patients back after a month to give them a second ablation if there was still residual disease and, if so, when was the starting point for your analysis with that cohort of patients? Second, did you evaluate other ultrasound characteristics of the lymph nodes aside from just size to see if any of them were associated with a better response to alcohol ablation?

Dr Veljko Strajina: What would typically happen when the patient comes to get an ablation is that a radiologist performs another ablation the following day if necessary. If they are happy with the results achieved, then they would see the patient in follow-up. Some of these patients did require a second ablation during that follow-up. Most patients did not. It would be exceptionally rare to have a third ablation. The clock starts when the radiologist thinks that a successful treatment of the lymph node has been achieved. So they had at least one "normal" ultrasound between the detection of recurrence and after the last ethanol ablation.