Editorial

Developing an algorithm for cost-effective, clinically judicious management of peripheral nerve tumors

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Abstract

Peripheral nerve tumors such as neurofibromas and schwannomas have become increasingly identified secondary to improved imaging modalities including magnetic resonance neurogram and ultrasound. Given that a majority of these peripheral nerve tumors are benign lesions, it becomes important to determine appropriate management of such asymptomatic masses. We propose a normal cost-effective management paradigm for asymptomatic peripheral nerve neurofibromas and schwannomas that has been paired with economic analyses. Specifically, our management paradigm identifies patients who would benefit from surgery for asymptomatic peripheral nerve tumors, while providing cost-effective recommendations regarding clinical exams and serial imaging for such patients.

Key Words: Cost-effectiveness, cost-utility outcomes, health-related quality of life, peripheral nerve tumors, neurofibromas, schwannomas

EDITORIAL COMMENTS

Practicing good medicine no longer means simply optimizing a clinical outcome but also requires efficiency through application of cost-effective methods. The development and widespread use of screening techniques is significantly increasing the detection of pathological lesions including peripheral nerve sheath nerve tumors. Unfortunately, similar advances in predicting the subsequent behavior of such mass lesions has not yet occurred. Lacking a clinical “crystal ball,” the best clinicians can do is to develop evaluation and treatment algorithms that balance the costs and benefits of following such masses with serial clinical exams and imaging studies against the risks, benefits, and costs of surgical treatment. This is exactly what the article by Birk et al. attempts to do. Such algorithms must take into account many factors and uncertainties, which make them a work in progress. Although a step in the right direction, they are imperfect models in need of constant revision and improvement.

A MAJOR CLINICAL DILEMMA: EVALUATION AND TREATMENT OF NEWLY DIAGNOSED PERIPHERAL NERVE TUMORS

The most common nerve sheath tumors, neurofibromas and schwannomas, are benign well-encapsulated neoplasms that demonstrate a limited capacity for infiltration into surrounding tissues. Peripheral nerve schwannomas affect nearly 200,000 people in the United States, whereas neurofibromas affect 1 in 30000 Americans and are associated with NF1 and NF2.

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mutations.\textsuperscript{[3]} Analogous to peripheral nerve sheath tumors and more commonly studied, intracranial vestibular schwannomas (VSs) have an incidence of 1.1 per 100,000 person-years, and their incidence has been steadily increasing in some countries like Denmark.\textsuperscript{[1,2]}

Analysis of the natural history and growth rate of these benign peripheral nerve tumors reveals that many do not grow, or may even stop growing naturally over time. Several studies show that anywhere from 58 to 69\% of both peripheral and central vestibular schwannomas treated conservatively do not grow during observation periods.\textsuperscript{[1,2,15]} Those that do enlarge grow at a very slow rate of only 0.9 mm to 2 mm per year.\textsuperscript{[1,6,8,13]} Another study found that the majority of VSs grew by <1 mm per year, with an overall mean rate of 1.2 mm/year.\textsuperscript{[14]} Another group reported that only 4 out of 70 patients >65 years of age required surgical intervention for intracranial vestibular schwannoma growth. Interestingly, one group even reported spontaneous tumor involution, or decrease in tumor size on imaging, for 6 out of 47 patients (13\%) followed for untreated unilateral vestibular schwannomas.\textsuperscript{[9]} Similar to schwannomas, neurofibromas may exhibit a slow natural growth pattern over time with growth cessation periods.\textsuperscript{[10]}

Given that the majority of peripheral nerve tumors are benign masses that grow slowly and may stop growing for very long periods of time, a major clinical dilemma arises when deciding how to appropriately manage asymptomatic peripheral nerve tumors. Widespread use of improved noninvasive imaging techniques has resulted in increased sensitivity in detecting nerve tumors. This has not been matched by improved specificity in determining which tumors will grow, become symptomatic, or even become malignant, versus which tumors will stop growing and remain asymptomatic. Just as increased rates of mammography and prostate-specific antigen screening have increased false positives for breast and prostate cancer treatment and led to unnecessary medical and surgical interventions,\textsuperscript{[2,10]} a similar dilemma faces the clinician who treats peripheral nerve tumors.

**ESTABLISHING A COST-EFFECTIVE TREATMENT PARADIGM FOR MANAGEMENT OF PERIPHERAL NERVE TUMORS**

Now that peripheral nerve tumors are more frequently identified with improved imaging techniques, the question arises as to how to most effectively distinguish which tumors will grow and cause symptoms from those that do not grow or grow at such a slow rate that the likelihood of symptom development is very small. Recent research in the realm of asymptomatic vestibular schwannomas supports a “wait-and-scan policy” with MRI scans performed annually for vestibular schwannoma surveillance.\textsuperscript{[7]} Specifically, a retrospective review of 576 patients revealed that 55\% of these tumors showed no growth over 5 years, and a total of 134 tumors (87\%) showed favorable growth patterns for conservative management. However, if tumors grow at a rate of >2.5 mm/year, then this is a strong predictor of eventual hearing deficits that would likely benefit from surgical intervention.\textsuperscript{[11,12]} We chose to apply a similar approach to the evaluation and treatment of newly diagnosed asymptomatic peripheral nerve tumors and combined it with economic analyses to determine an optimal cost-effective management paradigm for asymptomatic peripheral nerve schwannomas and neurofibromas.

To develop our paradigm, we first performed a retrospective review of the demographic and clinical characteristics, outcomes, and management costs for 35 peripheral nerve tumors patients who were either observed (n = 8) or surgically treated (n = 27) by a single surgeon (M.K.) at the University of California at San Francisco (UCSF) from January 2012 to December 2013 (Table 1). There was no statistically significant difference between the gender and age of the surgical and observation groups, although there was a trend toward older age in patients who were observed (52 vs. 44 years old, P = 0.271). The average tumor size in the surgical patients was significantly higher than the average tumor size of the observed patients (4.5 cm v. 2.7 cm; P < 0.01).

Health-related quality of life (HRQoL) was assessed in both cohorts of patients via pre and postoperative EQ-5D, a well-validated instrument for measuring generic health status on a scale of 0 to 1. On average, the surgical patients reported a significantly lower preoperative EQ-5D score as compared to the observation patients (0.576 vs. 0.757; P = 0.01). Following surgical resection, patients’ EQ-5D improved considerably, and their postoperative EQ-5D score was very similar to the most recent EQ-5D scores of patients who were observed (0.797 vs. 0.759, P = 0.298). Observation patients remained at similar EQ-5D scores at the beginning and end of the observation period (0.757 vs. 0.759).

We then performed a cost analysis of our observed versus surgically treated peripheral nerve tumor patients. For observed patients, we estimated the total cost for observation, allowing for either magnetic resonance neurograms (MRN) or ultrasound (U/S) imaging 3–6 months after the initial diagnostic scan, and then every 2 years afterwards if the tumor remained stable (Table 2; Figure 1). Actual office visit and imaging costs were determined from the UCSF hospital cost accounting database. These revealed total costs of $1090 and $580 in the first year of observation for patients receiving MRN versus U/S surveillance imaging, respectively (Table 2).
For surgical patients, the actual total inpatient and outpatient hospital costs were also determined from the UCSF hospital cost accounting database. The average total cost for treating peripheral nerve tumors surgically was $28465 [Table 2].

Next, we performed a cost-effectiveness analysis for a patient diagnosed with a peripheral nerve tumor at age 45 (the average age of our total patient cohort). We calculated quality-adjusted life years (QALYs) using our EQ-5D health utilities measure, and used a standard discounting factor of 0.03. Table 3 reveals that for a patient diagnosed with a peripheral nerve sheath tumor at age 45, surgery is associated with a higher lifetime cost ($28465). However, it produces a higher QALY than observation (17.95 vs. 16.84), resulting in surgery being a very cost-effective treatment option for peripheral nerve sheath tumor management. The incremental cost-effectiveness ratio (ICER) of $18687 is far below the standard cost-effectiveness threshold of $150,000 in the United States.\textsuperscript{[5,17]}

### Table 1: Demographics, clinical characteristics, and health-related quality of life outcomes for patients with peripheral nerve sheath tumors who were treated surgically (n=27) vs. observed (n=8)

| Characteristics          | Surgery ( # patients, % total) | Observation ( # patients, % total) |
|--------------------------|--------------------------------|-----------------------------------|
| Male vs. Female          | 17 (63%); 10 (37%)              | 5 (63%); 3 (37%)                  |
| Mean age (± SD)          | 44±19                           | 52±21                             |
| Race                     | Caucasian: 17 (63%)             | Caucasian: 7 (88%)                |
|                          | Hispanic: 3 (11%)               | Hispanic: 0 (0%)                  |
|                          | Asian: 3 (11%)                  | Asian: 1 (12%)                    |
|                          | Other: 4 (15%)                  | Other: 0 (0%)                     |
| Tumor size (Mean±SD)     | 4.5±2.53†                      | 2.7±2.6†                         |
| Tumor location           | Lower extremity: 7 (25%)        | Upper extremity: 2 (25%)          |
|                          | Upper extremity: 12 (44%)       | Upper extremity: 2 (25%)          |
|                          | Trunk: 8 (30%)                  | Trunk: 2 (25%)                    |
| Tumor pathology          | Schwannoma: 12 (44%),           | Schwannoma: 3 (37.5%)             |
|                          | Neurofibroma: 12 (44%)          | Neurofibroma: 3 (37.5%)           |
|                          | Unknown: 3 (12%)                | Unknown: 2 (25%)                  |

SD = standard deviation. †Statistically significant difference between groups by student’s t-test (P<0.01)

### Table 2: Cost breakdown for medically and surgically treated peripheral nerve tumors. All costs for imaging and office visits are based on UCSF costs

| First year | Cost | First year | Cost | First year | Cost |
|------------|------|------------|------|------------|------|
| Initial diagnosis-MRN | $462 | Initial diagnosis-U/S | $207 |
| Initial diagnosis-Office visit | $166 | Initial diagnosis-Office visit | $166 |
| 3–6 month MRN | $462 | 3–6 Month U/S | $207 |
| Total cost MRI observation in 1st year | $1090 | Total cost U/S observation in 1st year | $580 |
| Each additional 2 years | Total surgical cost in first year | $28465 |
| 1 Office visit | $166 | Each Additional 2 years | $166 |
| 1 MRI | $462 | U/S | $207 |
| Total cost MRI observation per 2 years | $628 | Total cost U/S observation per 2 years | $373 |

If gross total resection and no recurrence at 1 yr imaging | $0

Total surgical cost in first year represents average total hospital costs (inpatient+outpatient) for n=27 patients treated surgically for peripheral nerve sheath tumors at UCSF.

### Table 3: Cost-utility model if patient is diagnosed with peripheral nerve tumor at age 45. Total costs estimated over life expectancy of 36 additional years (from CDC life expectancy table), with 3% future discounting

| Treatment   | Cost | ΔCost | QALYs | ΔQALYs | ICER |
|-------------|------|-------|-------|--------|------|
| Observation | $7722 | 16.84 |       |        |      |
| Surgery     | $28465 | $20743 | 17.95 | 1.11 | $18687 |

QALY=Quality adjusted life year; ICER=Incremental cost-effectiveness ratio
CONCLUSION

In summary, we propose the following paradigm [Figure 1] to guide the management of symptomatic and asymptomatic peripheral nerve tumors. It is crucial to determine optimal frequency for clinical examinations and serial imaging studies, while also choosing the optimal imaging modality. Our management paradigm aims to identify patients upfront who would benefit from surgery (specifically, those harboring symptomatic and/or growing tumors), while providing a sensible and cost-effective set of recommendations regarding clinical exams and imaging studies for patients with asymptomatic nerve tumors whose growth rate is unknown.

An important limitation of our study is our small dataset, with the number of surgically treated patients being over three times larger than our medically treated patient cohort. This reflects the referral patterns to the neurosurgeon M.K. at a tertiary care facility. Another limitation is our study design, which is retrospective in nature. A more robust study would be prospective in nature and compare patients with peripheral nerve tumors that had equipoise, i.e. could be treated either medically or surgically. The lower EQ-5D and larger tumor size of our surgical group suggests that our patient cohorts were not identical in this small retrospective study.

Nevertheless, we find that surgery can be cost-effective in our patient cohort. We use our own institution’s cost data, as well as literature review and clinical experience, to propose a management guideline for newly diagnosed peripheral nerve sheath tumors, which we believe will be useful to the practicing neurosurgeon.

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