Friedman Aaron (Orcid ID: 0000-0001-5615-3442)
de Alarcon Alessandro (Orcid ID: 0000-0003-4792-4676)
Balakrishnan Karthik (Orcid ID: 0000-0002-0244-249X)
Novakovic Daniel (Orcid ID: 0000-0003-3839-1353)
Smith David (Orcid ID: 0000-0002-0048-4012)
Sidell Douglas (Orcid ID: 0000-0002-2088-6502)
Bock Jonathan (Orcid ID: 0000-0002-4367-7527)
Prager Jeremy (Orcid ID: 0000-0002-8123-2529)
Ongkasuwan Julina (Orcid ID: 0000-0001-8621-5456)
Meister Kara (Orcid ID: 0000-0002-4983-3068)
Leboulanger Nicolas (Orcid ID: 0000-0003-3466-6903)
Hamdi Osama (Orcid ID: 0000-0002-3495-9231)
Campisi Paolo (Orcid ID: 0000-0002-2750-8117)
Rinkel Rico (Orcid ID: 0000-0003-0056-7827)
Johnson Romaine (Orcid ID: 0000-0002-2322-5347)
Best Simon (Orcid ID: 0000-0001-8699-033X)
Wineland Andre (Orcid ID: 0000-0002-1576-3380)
Zur Karen (Orcid ID: 0000-0002-9045-6559)



# Title: Systemic bevacizumab for treatment of respiratory papillomatosis: international consensus statement

## Running Title: Systemic bevacizumab for papillomatosis

Douglas R. Sidell, MD[1,2]; Karthik Balakrishnan, MD, MPH [1,2]; Simon R. Best, MD [3]; Karen Zur, MD [4]; Julia Buckingham, MS[5]; Alessandro De Alarcon, MD [6]; Fuad M. Baroody, MD [7]; Jonathan M. Bock, MD [8]; Emily F. Boss, MD [9]; Charles M. Bower, MD [10]; Paolo Campisi, MD [11]; Sharon F. Chen, MD [12]; Jeffrey M. Clarke, MD [13]; Kevin D. Clarke, MD [14]; Alejandro Cocciaglia, MD [15]; Robin T. Cotton, MD [6]; Giselle Cuestas, MD [16]; Kara L. Davis, MD [17]; Victor Hugo DeFago, MD [18]; Frederik G. Dikkers, MD [19]; Ines Dossans, MD [20]; Walter Florez, MD [21]; Elizabeth Fox, MD [22]; Aaron D. Friedman, MD [23]; Nazaneen Grant, MD [24]; Osama Hamdi, BS[25]; Norman D. Hogikyan, MD [26]; Kaalan Johnson, MD [27]; Liane B. Johnson, MD [28]; Romaine F. Johnson, MD [29]; Peggy Kelly, MD [30]; Adam M. Klein, MD [31]; Claire M. Lawlor, MD [32]; Nicolas Leboulanger, MD [33]; Alejandro G. Levy, MD [34]; Derek Lam, MD [35]; Greg R. Licameli, MD [36]; Steve Long, MD [37]; David G. Lott, MD [38]; Dayse Manrique, MD [39]; J. Scott McMurray, MD [40]; Kara D. Meister, MD [1,2]; Anna H. Messner, MD [41]; Michael Mohr, MD [42]; Pamela Mudd, MD [32]; Anthony J. Mortelliti, MD [43]; Daniel Novakovic, MD [44]; Julian Ongkasuwan, MD [45]; Shazia Peer, MD [46]; Krysztof Piersiala, MD [47] Jeremy D. Prager, MD [30]; Seth M. Pransky, MD [48]; Diego Preciado, MD [32]; Tiffany Raynor, MD [49]; Rico N.P.M. Rinkel, MD [50]; Hugo Rodriguez, MD [51]; Verónica P. Rodríguez, MD [16]; John Russell, MD [52]; María Laura Scatolini, MD [51]; Patrick Scheffler, MD [1]; David F. Smith, MD [53]; Lee P. Smith, MD [54]; Marshall E. Smith, MD [55]; Richard J.H. Smith, MD [56]; Abraham Sorom, MD [57] Amalia Steinberg, MD [58]; John A. Stith, MD [59]; Dana Thompson, MD [60]; Jerome W. Thompson, MD [61]; Patricio Varela, MD [62]; David R. White, MD [63]; Andre M. Wineland, MD [9]; Christina J. Yang, MD [64]; Carlton J. Zdanski, MD [65]; Craig S. Derkay, MD [66].

[1]Department of Otolaryngology-Head & Neck Surgery, Stanford University School of Medicine, Stanford, CA, USA; [2]Aerodigestive and Airway Reconstruction Center, Lucile Packard Children's Hospital Stanford. Stanford, CA, USA; [3]Department of Otolaryngology- Head and

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/lary.29343

Neck Surgery, Division of Laryngology, and, Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD, USA;[4] Division of Pediatric Otolaryngology, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [5]Maternal and Child Health Research Institute, Lucile Packard Children's Hospital, Stanford University School of Medicine, Stanford University, Stanford, CA, USA; [6]Department of Otolaryngology, Division of Pediatric Otolaryngology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [7]Section of Otolaryngology-Head and Neck Surgery and Department of Pediatrics, University of Chicago Medicine and The Comer Children's Hospital, Chicago, IL, USA; [8]Department of Otolaryngology & Communication Sciences, Division of Laryngology & Professional Voice, Medical College of Wisconsin, WI, USA; [9]Department of Otolaryngology-Head and Neck Surgery and the Department of Health Policy and Management, Division of Pediatric Otolaryngology, Johns Hopkins University School of Medicine, Baltimore, MD, US; [10]Department of Otolaryngology Head and Neck Surgery, Division of Pediatric Otolaryngology, University of Arkansas for Medical Sciences (UAMS), Arkansas Children's Hospital, Little Rock, AK, USA; [11]Department of Otolaryngology – Head & Neck Surgery, Hospital for Sick Children, University of Toronto, Toronto, Canada; [12]Department of Pediatrics, Division of Infectious Diseases. Lucile Packard Children's Hospital Stanford, Stanford, CA, USA; [13]Department of Medicine, Division of Oncology; Duke Cancer Institute, Duke University School of Medicine , Durham, NC, USA; [14]Pediatric Otolaryngology, Division of Otolaryngology Head and Neck Surgery, University of British Columbia (UBC, UVIc),Victoria General Hospital, BC, Canada; [15] ENT-Respiratory Endoscopy Department, Garrahan Children's Hospital, Buenos Aires, Argentina; [16]Respiratory Endoscopy Section, ENT Department, Hospital General de Niños "Dr. Pedro de Elizalde", Buenos Aires, Argentina; [17]Department of Pediatrics, Division of Pediatric Oncology, Bass Center for Childhood Cancer and Blood Disorders, Stanford University, Stanford, CA, USA; [18]Pediatric Surgery, Sanatorio del Salvador Privado SA, Cordoba, Argentina; [19]Department of Otorhinolaryngology, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands; [20]Otolaryngology-Head and Neck Surgery, Hospital Pereira Rossell, Montevideo, Uruguay; [21]Department of Otolaryngology, Instituto Nacional de Salud del Niño de San Borja, Lima, Perú; [22]Comprehensive Cancer Center, St Jude Children's Research Hospital, Memphis, TN, USA; [23]Department of Otolaryngology, Head and Neck Surgery, University of Cincinnati School of Medicine, Cincinnati, OH, USA; [24]Department of Otolaryngology, Division of Laryngology, Medstar Georgetown University Hospital, Georgetown, Washington, DC, USA; [25]Howard University College of Medicine, Washington, DC, USA; [26]Department of Otolaryngology- Head and Neck Surgery, University of Michigan Medical School, Ann Arbor, MI, USA; [27]University of Washington School of Medicine, Department of Otolaryngology Head and Neck Surgery, Division of Pediatric Otolaryngology, Seattle, WA, USA; [28]Department of Surgery, Dalhousie University, Division of Paediatric Otolaryngology-Head and Neck Surgery, IWK Health Centre, Halifax, Nova Scotia; [29]Department of Otolaryngology-Head and Neck Surgery, University of Texas (UT) Southwestern Medical Center, Dallas, TX, USA; [30]Department of Otolaryngology, Head and Neck Surgery, Division of Pediatric Otolaryngology, Children's Hospital Colorado affiliated with University of Colorado, Anschutz, Aurora, CO; [31]Department of Otolaryngology-Head and Neck Surgery, Division of Laryngology, Emory Voice Center, Emory University School of Medicine, Atlanta, GA, USA; [32]Department of Otolaryngology, Division of Pediatric Otolaryngology, Children's National Health System, George Washington University School of

Medicine, Washington, DC, USA; [33]Head and Neck Surgery, Pediatric Otolaryngology, Necker Enfants Malades Hospital, Paris University, Paris, France; [34]Department of Pediatrics, Division of Pediatric Hematology and Oncology. Arnold Palmer Hospital Center for Children's Cancer and Blood Disorders. Orlando Health. Orlando, FL, USA; [35]Department of Otolaryngology-Head and Neck Surgery, Oregon Health and Science University, Portland, OR, USA; [36]Department of Otolaryngology, Boston Children's Hospital. Boston, MA, USA; [37]Department of Head and Neck Surgery. Kaiser Permanente, Hillsboro, OR, USA; [38]Department of Otorhinolaryngology, Division of Laryngology, Mayo Clinic Arizona, Phoenix, AZ, USA; [39]Department of Otorhinolaryngology, Universidad Federal de Sao Paulo (UNIFESP), Sao Paulo, Brazil; [40]Pediatric Otolaryngology, University of Wisconsin School of Medicine and Public Health. Madison, WI, USA; [41]Department of Otolaryngology/Head & Neck Surgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USA; [42]Department of Hematology, Oncology and Respiratory Medicine, University Hospital Muenster, Muenster, Germany; [43]Department of Otolaryngology- Head and Neck Surgery, State University of New York (SUNY) Upstate Medical University, Syracuse, NY, USA; [44]Department of Otolaryngology, Head and Neck Surgery. Central Clinical School, Faculty of Medicine and Health, University of Sydney, The Canterbury Hospital. Sydney, Australia; [45]Department of Otolaryngology, Division of Adult and Pediatric Laryngology, Bobby R. Alford Department of Otolaryngology Head and Neck Surgery, Baylor College of Medicine, Texas Children's Hospital. Houston, Tx, USA; [46]Division of Otorhinolaryngology, University of Cape Town & Red Cross War Memorial Children's Hospital, Cape Town, South Africa; [47]Division of Ear, Nose and Throat Diseases, Karolinska Institutet, Karolinksa University Hospital, Stockholm, Sweden; [48]Rady Children's Hospital. San Diego, CA, USA; [49]Department of Otolaryngology, Head and Neck Surgery, Texas Children's Hospital, Baylor College of Medicine. Houston, TX, USA; [50]Department of Otolaryngology, Amsterdam UMC, Vrije Universiteit Amsterdam. Amsterdam, Netherlands; [51]Respiratory Endoscopy Department, Hospital de Pediatria Prof Dr. Juan P. Garrahan, Buenos Aires, Argentina; [52]Department of Paediatric Otolaryngology, Children's Health Ireland, (Crumlin ), Dublin, Ireland; [53]Divisions of Pediatric Otolaryngology, Pulmonary Medicine, and the Sleep Center, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, OH, USA; [54]Division of Otolaryngology-Head and Neck Surgery, Pediatric Otolaryngology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Steven and Alexandra Cohen Children's Medical Center of New York, New Hyde Park, NY, USA; [55]Division of Otolaryngology-Head and Neck Surgery, University of Utah School of Medicine, Salt Lake City, UT, USA; [56]Department of Otolaryngology-Head and Neck Surgery, University of Iowa Hospitals and Clinics, Iowa, USA; [57]Otolaryngology, Head and Neck Surgery, Confluence Health, Wenatchee, WA, USA; [58]Otolaryngology, Head and Neck Surgery, Alaska Native Medical center, Anchorage, AK, USA. [59]Department of Otolaryngology-Head and Neck Surgery, Division of Pediatric Otolaryngology, SSM Cardinal Glennon Children's Hospital Medical Center, St. Louis, MO, USA; [60]Division of Pediatric Otolaryngology Head and Neck Surgery Ann & Robert H Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [61]University of Tennnessee, College of Medicine, Department of Otolaryngology-Head and Neck Surgery, Division of Pediatric ENT, LeBonheur Children's Hospital, Memphis TN, USA; [62]Pediatric Surgery Department. Universidad de Chile , Mackenna Children Hospital, Clinica Las Condes Medical center, Santiago, Chile; [63]Division of Pediatric Otolaryngology, Medical University of South Carolina (MUSC) Shawn Jenkins Children's Hospital. Charleston, SC, USA;[64]Department of

Otolaryngology- Head and Neck Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Children's Hospital at Montefiore. New York, NY, USA; [65]Department of Otolaryngology/Head and Neck Surgery, Division of Pediatric Otolaryngology/Head and Neck Surgery, North Carolina Children's Hospital, University of North Carolina at Chapel Hill, USA; [66]Department of Otolaryngology-Head and Neck Surgery, Eastern Virginia Medical School, Children's Hospital of the King's Daughters.

**Funding and conflicts of interest:** No disclosures

**Corresponding author:** Douglas R. Sidell, MD; Otolaryngology-Head & Neck Surgery, Division of Pediatric Otolaryngology, Stanford University School of Medicine. 801 Welch Road, Stanford, CA 94305, Tel (650) 724-4800, dsidell@stanford.edu

Acknowledgement: The authors would like to acknowledge research support provided by the Maternal and Child Research Institute, Lucile Packard Children's Hospital Stanford, Stanford University School of Medicine.

**Abstract**

**Objectives:** The purpose of this study is to develop consensus on key points that would support the use of systemic bevacizumab for the treatment of recurrent respiratory papillomatosis (RRP), and to provide preliminary guidance surrounding the use of this treatment modality.
**Methods:** A multidisciplinary, multi-institutional panel of physicians with experience using systemic bevacizumab for the treatment of RRP was established. The Delphi method was used to identify and obtain consensus on characteristics associated with systemic bevacizumab use across five domains**:** 1) patient characteristics; 2) disease characteristics; 3) treating center characteristics; 4) prior treatment characteristics; and 5) prior work-up.
**Results:** The international panel was composed of 70 experts from 12 countries, representing pediatric and adult otolaryngology, hematology/oncology, infectious diseases, pediatric surgery, family medicine, and epidemiology. A total of 189 items were identified, of which consensus was achieved on Patient Characteristics (9), Disease Characteristics (10), Treatment Center Characteristics (22), and Prior Workup Characteristics (18)
**Conclusion:** This consensus statement provides a useful starting point for clinicians and centers hoping to offer systemic bevacizumab for RRP and may serve as a framework to assess the components of practices and centers currently using this therapy. We hope to provide a strategy to offer the treatment and also to provide a springboard for bevacizumab's use in combination with other RRP treatment protocols. Standardized delivery systems may facilitate research efforts and provide dosing regimens to help shape best-practice applications of systemic bevacizumab for patients with early-onset or less-severe disease phenotypes.

**Keywords:** systemic bevacizumab; Avastin; consensus

**Level of Evidence:** 5

## Introduction

HPV-associated recurrent respiratory papillomatosis (RRP) is the most common benign airway neoplasm, with estimated incidence of 4.3/100,000 children and 3-4/100,000 adults annually, though this figure is declining.[1-5] While RRP incidence and prevalence have declined in countries with widespread access to the HPV vaccine, many countries continue to suffer intense RRP burden. Although mortality in the United States is often the consequence of pulmonary disease, in many countries, laryngeal obstruction may remain a dominant source of mortality. To date, there is no cure.

Surgical excision/debridement remains the gold standard treatment, though various topical, intralesional, and systemic adjuvant therapies have been tried.[1,6] Unfortunately, these therapies are not universally effective, and each has an associated risk profile. [1,6-9]

### *RRP and bevacizumab*

Vascular growth appears to be a universal pathophysiologic contributor to RRP proliferation and recurrence. Selective vascular ablation using KTP (potassium titanyl phosphate) laser concurrent with surgical debridement has shown promise in reducing recurrence.[7] Similarly, intralesional inhibition of vascular endothelial growth factor (VEGF) in RRP patients has demonstrated reductions in disease recurrence and frequency of surgical debridement required.[7-9]

Bevacizumab, a recombinant VEGF-binding antibody that inhibits interaction with the VEGF receptor, has been used for over 15 years as systemic chemotherapy to inhibit vascular growth associated with metastatic malignancy. It has also been administered locally in patients with hereditary hemorrhagic telangiectasias and in children with retinopathy of prematurity.[8] Off-label intralesional injection of bevacizumab at the time of surgical debridement reduces RRP burden and surgical frequency in select children and adults.[1,6-9] Unfortunately, this strategy does not benefit all patients and is impractical for diffuse tracheal disease or pulmonary lesions.

Systemic administration of bevacizumab for RRP was first reported in 2009. Nagel and colleagues described a 32-year-old male with pulmonary and tracheal disease requiring laser-debridement four times a year over a 10-year period. The patient had significant regression of his papilloma following systemic administration of bevacizumab.[2] In 2014, Mohr and colleagues presented 5 patients with advanced tracheal papillomatosis treated with systemic bevacizumab. All patients demonstrated rapid and dramatic improvement of disease burden.[10] In 2016, Zur and Fox used systemic bevacizumab for extensive pulmonary and laryngotracheal papillomatosis in a 12-year old tracheostomy-dependent child with refractory disease, describing complete laryngeal disease resolution after three months of treatment. The patient was ultimately decannulated and remains free of gross disease with interval infusions.[11]

Subsequently, a nationwide survey identified variability in treatment dosing, treatment frequency, and degree of response. The authors concluded that systemic bevacizumab showed significant promise in patients with advanced, treatment-resistant papillomatosis. [12]

These data suggest systemic bevacizumab may be an important option for patients with severe or otherwise life-threatening disease resistant to other therapies. Nevertheless, many facets of treatment remain undetermined. This study aimed to develop consensus on key points of patient selection, disease attributes, and treatment center characteristics appropriate for the use of systemic bevacizumab. We used a modified Delphi approach to identify and survey an

international body of physicians with expertise in RRP treatment and experience using systemic bevacizumab to treat RRP.

## METHODS

The Delphi method provides a structured approach to achieve expert consensus in the absence of adequate data to guide situational assessment and decision-making.[13] This method has proved useful in addressing a range of healthcare questions.[14,15] Previously described approaches have either used direct discussion between expert panelists (in person or via telephone) or have avoided discussion[14,15]. This design is based on previously published work.[15] This study was reviewed and exempted by the Stanford University Institutional Review Board.

Statistical analysis was performed using Excel 2010 (Microsoft Corp, Redmond, Washington). Web-based surveys used Qualtrics (Qualtrics, Provo, UT). Surveys were distributed by email via individualized links. This non-human-subjects survey was exempt from IRB-review.

### Identifying study participants

We used a snowball sampling strategy, first identifying individuals with experience treating, or planning to treat, adults or children with RRP using systemic bevacizumab. An initial email contacted approximately 250 individuals identified as potential experts in the field by the study facilitators and lead authors through several different mechanisms (social media channels, web groups, patient organizations, working group lists, prior publications, and direct knowledge of invitees' work). Individuals were asked to confirm their experience and their interest in participating and were allowed to also suggest other participants. Inclusion criteria included individuals who responded to the survey; agreed to participate in the study; and confirmed a history of, or planned future use of, systemic bevacizumab for RRP during the study period. All surveys and invitation emails were sent in English. Individuals who did not respond to the survey, declined to participate, could not participate due to language barrier, or did not have experience using systemic bevacizumab to treat RRP were excluded.

### Modified Delphi process

The multidisciplinary, international group of experts responded to a web-based survey asking them to propose factors to be considered or adhered to when using systemic bevacizumab. Respondents were asked to list 5-15 characteristics within each of five domains: 1) patient characteristics; 2) disease characteristics; 3) treating center characteristics; 4) prior treatment characteristics; and 5) prior work-up. Respondents could also propose additional domains.

Open-ended responses were consolidated and organized by theme. This process included combining responses with identical meanings, re-wording or re-phrasing responses for clarity, and translating responses to the English language. Facilitators with experience in the treatment of RRP and in using the modified Delphi method worked to preserve intent of the study group's responses. Each survey was sent with a two week requested response time and one reminder sent during the response period.

From analyses of consolidated and anonymized responses, a new survey was generated and sent to respondents. This survey comprised statements that participants were directed to rate for relevance in treatment decision-making. Statements were either those that required the choice of a single statement (e.g. "Please evaluate the following two statements. Please choose the statement that you agree with the most regarding the patient's age at the time of onset of RRP"), or those that required rating a statement for importance. Respondents were thus instructed to rate items on a 1-9 Likert scale (9 = most important) or presented forced-choice questions (choose one statement). Facilitators directed respondents to distinguish between rating items important to consider before starting bevacizumab, versus rating items that would increase the chance of using bevacizumab. To this end, instructional text was added to each segment of questions: "If you are more likely to administer bevacizumab to a patient that has had multiple life-threatening airway issues, you would rate this as more important on the 1-9 scale - even if it were not something that would need to be present before you started treatment". We calculated mean, median, mode, maximum and minimum rating for each item.

Based on predetermined cutoffs established in previous Delphi consensus statements,[14,15] we established *a priori* criteria for consensus (mean rating $\geq 7$, with $\leq 1$ response $\geq 2$ points away from mean) and near consensus (mean rating $\geq 6.5$, with $\leq 2$ responses $\geq 2$ points away from mean).

For results of forced choice questions (choose one statement), we calculated percentage of respondents for each statement and defined consensus as a supermajority of $\geq 75\%$ and near consensus as $\geq 66\%$ (and not reaching supermajority status).[14,15]

Summary data (mean, median, mode, maximum and minimum; or percentage of respondents for forced choice questions) of the previous Delphi survey were provided in an Excel sheet to each study group member prior to subsequent survey rounds. Respondents were directed to consider the previous survey results when rerating a statement. The mean and median from the most recent round of results were included within the survey at the end of each statement. A total of four survey rounds were completed.

## RESULTS

### *International Body of Experts*

Over the duration of the study, all 70 individuals participated at the pre-determined minimum required level of completion (at least 50% of surveys). The final working group represented 12 countries and 56 institutions. The study group comprised pediatric and adult otolaryngologists (n=61), adult and pediatric hematologist-oncologists (n=6), pediatric surgeons (n=2), pediatric infectious disease (n=1), and one provider with family medicine and epidemiology training.

### *Summary of Responses*

A total of 189 characteristics were identified, including 185 items requiring rating, and four forced-choice items. A total of 56 rated items met consensus criteria, 14 items near-consensus, and 114 items were excluded (Table 1). Forced-response items are shown in Table 2. Eliminated items are shown in Appendix, Table 1.2 and Table 2.2.

Domain 1 outlined patient characteristics and consisted of 4 groups representing 20 characteristics and two forced-choice questions. Forced choice items were related to both age at the time of diagnosis and age at the time of surgery; the majority of respondents felt that age should not influence use of systemic bevacizumab.

Domain 2 outlined key disease characteristics associated with 1) location and/or appearance of disease, 2) disease severity and/or progression of disease, 3) papilloma staging system/score and 4) histopathology and virology.

Domain 3 clarified treatment center characteristics recommended for safe systemic bevacizumab use. Of 40 items initially submitted, 21 met consensus criteria, 3 near-consensus, and 16 were eliminated. The domain was divided into five groups including: 1)availability of specific specialists at the treating center 2) availability of specific services, 3) availability of specific facilities, 4) availability of a tumor board and/or multidisciplinary treatment group and 5) research infrastructure/data collection.

Domain 4, Prior Treatment, was divided into three groups, focusing on prior non-surgical interventions (Group 1) and prior surgical interventions (Groups 2 and 3). Eleven initially identified characteristics in Group 1 were all eliminated. Groups 2 and 3 contained forced-choice questions addressing frequency and number of prior surgical interventions. While frequency of prior surgical interventions was felt to important by the majority of participants, total number of prior interventions was not.

Finally, domain 5 dealt with prior workup. It was divided into 13 groups. 75 characteristics were initially identified, with 18 meeting consensus criteria, 5 near-consensus, and 52 eliminated. The majority of consensus items related to pre-treatment laboratory evaluation, with additional consensus items associated with preoperative airway evaluation, referral and consulting services, and general health history requirements.

## DISCUSSION

This investigation identified and prioritized characteristics of patients who may benefit from systemic bevacizumab therapy while minimizing treatment risks, as well as elements of care systems that might promote safe administration, including prior patient workup, treatment center factors, and care providers administering therapy. Importantly, those items that met consensus were should not be identified as essential components prior to the initiation of therapy, but instead suggestions of ideal-state considerations for IV bevacizumab use.

Mounting evidence supports the use of systemic bevacizumab for RRP treatment. However, high-level studies and clinical trials are lacking, and it remains an off-label indication while risks and benefits continue to be elucidated. The majority of centers participating in this study treat only a small cohort of individuals, and practice patterns vary between institutions. Case reports have focused on patients with severe, recidivistic disease and a longstanding history of surgical intervention.[10-12] These reports have served as a foundation for the use of systemic bevacizumab for RRP, but practice patterns are often extrapolated from an admixture of oncologic indications and previous anecdotal experience. As such, variability in dosing, frequency, and the timing of surgical debridement persist. This variability may be an obstacle to institutions and clinicians considering offering this treatment option. Patients may then be sent to centers with prior experience using systemic bevacizumab for RRP or denied a potentially beneficial treatment, reducing access to potentially lifesaving therapy.

We thus hope to provide a standardized and consistent infrastructure and patient selection framework for centers that currently provide, or may in future provide, systemic bevacizumab therapy for RRP. This investigation is an early step in the investigation of appropriate systemic bevacizumab use for patients with RRP; it does not address dosing protocols, timing of surgical interventions, or management of patients in remission or relapse. Several salient points merit mention.

*Patient Characteristics*

The consensus suggests that age at surgery or at time of diagnosis should not be a deciding factor in the treatment of patients with RRP. No available information suggests this treatment should be withheld or administered based on age alone; both pediatric and adult patients have seen both partial benefit and complete remission from disease.[10-12] Patients should adhere to the following: 1. undergo laryngoscopy and bronchoscopy to manage disease as needed during the treatment period, 2. agree to off-label use of the medication with informed consent, and 3. avoid pregnancy and lactation during and surrounding the treatment period.

*RRP Treatment History*

No single characteristic of past surgical or non-surgical RRP treatment met consensus criteria. The total number of past surgical interventions was also not important. In contrast, frequency of surgical interventions should be considered prior to initiating systemic bevacizumab treatment. The consensus suggested that rapidity of papilloma re-accumulation may represent disease severity better than longevity of disease.

*Disease Characteristics*

Several consensus and near-consensus items overlapped. For example, consensus items supporting systemic bevacizumab use included progressive and/or severe disease burden, and disease in locations difficult to treat with standard surgical intervention. Similar items achieving near-consensus included need for tracheostomy or long-term ventilatory support due to disease burden, rapidly progressing or rapidly enlarging bulky disease, and increasing Derkay score over the preceding year. This suggests that patients with tracheostomy or long-term mechanical ventilation due to disease burden or disease progression over the preceding year may still be candidates for treatment, but that these items in isolation do not necessarily make practitioners more likely to use systemic medication. Although the general use of a staging system to describe RRP burden prior to initiation of systemic bevacizumab met near-consensus criteria, a specific staging system was not agreed upon. Nevertheless, documentation of endoscopic and clinical examination findings can be considered reasonable, the use of a specific staging system (e.g. Derkay score) notwithstanding.

*Prior Evaluation/Workup*

This section aimed to describe optimal patient preparation and evaluation prior to initiating systemic bevacizumab therapy. Overall, the working group felt that an oncology service should determine, order, and evaluate all laboratory studies prior to initiating systemic

bevacizumab. Of eight laboratory studies meeting consensus for being *checked* before initiating treatment, only the complete blood count (CBC) was recommended to be *normal* prior to treatment, possibly owing to the bleeding risk associated with systemic bevacizumab. To date, anecdotal accounts of bleeding following systemic bevacizumab use for RRP are limited to bloody sputum or bloody secretions following debridement of papilloma on the day of infusion. As a precaution, bevacizumab infusions are often given on the day of surgical debridement after the procedure, or a few days later.

The requirement for chest computed tomography (CT) prior to systemic bevacizumab met near-consensus criteria, however no single imaging study met consensus. It would thus be reasonable to make the decision to perform pretreatment radiologic studies on a patient-by-patient basis. Many patients with extra-laryngeal disease have undergone chest CT, and this would be reasonable in any patient at risk of pulmonary involvement.[10-12]

Finally, the working group supported diagnostic laryngoscopy and bronchoscopy in the operating room prior to initiating systemic bevacizumab therapy. For studies on papilloma tissue, consensus was reached for both human papilloma virus typing and evaluation for malignancy. We suggest that understanding of the presence, location, and histologic characteristics of disease is important before initiating systemic therapy.

*Treating Facility and Personnel*

Because a key premise of this investigation was to optimize safe patient care, it is important to understand facility and personnel characteristics important to this process. Participants felt that systemic bevacizumab administration is best done at centers able to assess and promptly manage complications or adverse effects. Consensus was reached on the necessity of specialists capable of assessing the disease anatomically and histologically and providing age-appropriate care for pediatric patients. Importantly, consensus was reached that multidisciplinary coordinated team care is necessary.

*Final Considerations*

As with any consensus statement, this study has important limitations. First, it is based on expert opinion, though obtained and developed through standardized and structured methods. The results are therefore vulnerable to biases in individual respondents, though these may be countered by the Delphi method of leveraging “groupthink” bias to achieve convergence and consensus. Second, *a priori* criteria for consensus and near consensus, while necessary, may eliminate apparently sensible items. This result may be useful in that it questions conventional wisdom, but it also means that this consensus statement should be taken as a foundation rather than a final set of criteria for safe and effective bevacizumab use. Eliminated items should not necessarily be seen as unimportant. Heterogeneity of specialties and geographic practice settings may also have prevented some consensus, though the advantage is a better representation of viewpoints. Finally, not all possible countries and specialties were included, which may also introduce biases. From a public health standpoint, this consensus may make access to systemic bevacizumab more challenging if widely adopted, because it recommends treatment at high-level facilities less accessible in resource-limited areas.

## CONCLUSION

This consensus statement provides guidance for clinicians planning to offer systemic bevacizumab, and for clinicians and centers already offering bevacizumab who want to assess and optimize their practice. Although it is not intended to define absolute prerequisite criteria for the use of IV bevacizumab, we do hope that clinicians will find this document useful in structuring patient selection and workup, treatment administration practices (independent of specific dosing regimens), and center design, as they consider the key questions of which patients are likely to benefit, which patients are likely safe to receive treatment, and how to optimally deliver this treatment. This report also provides a structure to allow additional centers to offer this treatment and may facilitate bevacizumab use in combination with other RRP treatment protocols. Standardized delivery systems will also allow future multi-institutional research efforts, including dosing regimens, which were not studied here. These results may also guide best-practice applications of systemic bevacizumab in selected patients with early-onset or less-severe disease phenotypes. Finally, this may stimulate the formation of an international patient registry to prospectively track patient characteristics and outcomes following systemic bevacizumab therapy, and to allow systematic evaluation of this therapy over time.

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Table Legends:
Legends to tables.

Table 1: List of items to identify and obtain pre-determined consensus on characteristics associated with systemic bevacizumab use for the treatment of RRP across five domains using a modified Delphi method. 56 rated items met consensus criteria, and 14 items met near-consensus criteria.

Consensus: mean rating ≥ 7, with ≤ 1 response ≥ 2 points away from mean.
Near consensus: mean rating ≥ 6.5, with ≤ 2 responses ≥ 2 points away from mean.
*: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Table 2: Forced-response items on characteristics associated with systemic bevacizumab use for the treatment of RRP across two domains using a modified Delphi method.
Consensus: supermajority of ≥ 75% of respondents
Near consensus as ≥ 66% (and not reaching supermajority status).

Appendix:

Table 1.2: List of eliminated items to identify and obtain pre-determined consensus on characteristics associated with systemic bevacizumab use for the treatment of RRP across five domains using a modified Delphi method. These 114 items were eliminated because they did not achieve consensus or near-consensus according to pre-determined criteria.
Consensus: mean rating ≥ 7, with ≤ 1 response ≥ 2 points away from mean.
Near consensus: mean rating ≥ 6.5, with ≤ 2 responses ≥ 2 points away from mean.

Table 2.2. Eliminated forced-response items on characteristics associated with systemic bevacizumab use for the treatment of RRP across two domains using a modified Delphi method.
Consensus: supermajority of ≥ 75% of respondents
Near consensus as ≥ 66% (and not reaching supermajority status).

| Table 1 Consensus and Near Consensus Statements (Likert Scale) | | |
|---|---|---|
| **Domain 1. Patient Characteristics** | | |
| Group | Statement | Consensus Status |
| 1. Social and Demographic Characteristics | Significant reduction in patient's quality of life | **Consensus** |
| | Patient is able to adhere to treatment regimen including blood work/serology/checkup schedule | **Consensus** |
| | Patient is able to undergo repeated laryngoscopy and bronchoscopy | **Consensus** |
| | Patient or legal guardian/parent are agreeable to off-label medication use | **Consensus** |
| | Patient is not pregnant or lactating | **Consensus** |
| | Patient is not planning on becoming pregnant during or for 6 months after end of treatment | **Consensus** |
| 2. Lack of standard of care option | Patient has significant risk of difficult airway/airway obstruction with anesthesia | **Consensus** |
| **Domain 2. Disease Characteristics** | | |
| Group | Statement | Consensus Status |
| 1. Location and/or appearance of disease | Progressive pulmonary disease by serial chest computed tomography (CT) imaging (≥ 20% increase by RECIST 1.1 criteria on 2 subsequent scans at least 3 months apart) | **Consensus** |
| | Primarily tracheobronchial or pulmonary parenchyma | **Consensus** |
| | Disease extends beyond upper 1/3 of trachea | **Consensus** |
| | Involves upper, middle, and lower trachea | **Consensus** |
| | Esophageal and tracheal involvement | **Consensus** |
| | ANY extralaryngeal extension (pharynx, esophagus, trachea, bronchus, lung) | **Consensus** |
| | Disease in locations difficult to treat by standard techniques | **Consensus** |
| 2. Disease severity and/or progression of the disease | Recurrent or multiple documented events of respiratory distress | **Consensus** |
| | Rapid progression of disease beyond the larynx | **Consensus** |
| | Patient has required emergent airway management more than one time prior to performing operative treatment to remove papilloma | **Consensus** |
| | Tracheostomy due to disease burden | *Near consensus* |
| | Long-term ventilation due to disease burden | *Near consensus* |
| | Rapidly progressing or rapidly enlarging bulky disease | *Near Consensus* |
| 3. Papilloma staging system/score | A recurrent respiratory papillomatosis staging system should be used to describe papilloma burden prior to the use of systemic bevacizumab (Avastin) | *Near Consensus* |
| 4. Histopathology and Virology of the disease | Malignant transformation present | *Near consensus* |
| | Cytologic dysplasia or atypia present | *Near consensus* |

| Domain 3. Treatment Center Characteristics | | |
|---|---|---|
| Group | Statement | Consensus Status |
| Presence and/or availability of the following *specialists* are at the treating center | Otolaryngologist is available. If the patient is a child/pediatric patient then the treating center should have pediatric otolaryngologist available | **Consensus** |
| | If there is pulmonary disease, pulmonologist is available | **Consensus** |
| | Oncologist is available. If the patient is a child/pediatric patient then the treating center should have pediatric oncologist available | **Consensus** |
| | Pathologist is available for tissue diagnosis, evaluation for dysplasia | **Consensus** |
| | The otolaryngologist present has experience managing patients with recurrent respiratory papillomatosis | **Consensus** |
| | The practitioners/oncologists at treating center have experience giving systemic bevacizumab (Avastin) (for any indication) and/or treating the side-effects of systemic bevacizumab (Avastin) | **Consensus** |
| | The treating center treats multiple patients with ongoing or active RRP | *Near consensus* |
| Presence and/or availability of the following outpatient and/or inpatient *services* at the treating center | Radiology services | **Consensus** |
| | Oncology services | **Consensus** |
| | Internal medicine or pediatric care services | **Consensus** |
| | Center has experienced chemotherapy nurses | **Consensus** |
| | An outpatient infusion center or infusion day-clinic is available | **Consensus** |
| | The center has designated intensive care unit (ICU) or a pediatric ICU (PICU) if the patient is a child | **Consensus** |
| | If pediatric patient, the center has pediatric anesthesiologists and or pediatric surgical specialists | **Consensus** |
| | The center is a tertiary care medical center | **Consensus** |
| | The center has an otolaryngology team capable of age-appropriate complex airway management | **Consensus** |
| | The center is able to admit/hospitalize the patient during the administration of medication if needed | **Consensus** |
| | The center has an anesthesia team with specific skills and experience in managing patients with respiratory papilloma | **Consensus** |
| | The center is able to maintain close communication with local oncologists if they are not present at the primary treating center | *Near consensus* |
| Facilities present at the treating center | A certified pharmacy is accessible before and after treatment | **Consensus** |
| | Capable of monitoring the patient during systemic infusions | **Consensus** |
| | Ability to perform transfusions in the event of bleeding | **Consensus** |

| | | |
|---|---|---|
| Tumor board/multidisciplinary treatment group | The center has a multidisciplinary follow-up with all available services as needed: (pediatrics, infectious disease, oncology, hematology, otorhinolaryngology, pneumonology/pulmonary medicine) | **Consensus** |
| Research infrastructure/data collection | The treating center has the capacity to participate in a clinical study or trial of off-label use of medication | *Near Consensus* |
| **Domain 4. Prior Treatment Characteristics**** | | |
| **All proposed statements (Likert criteria) in Domain 4 were eliminated | | |
| **Domain 5. Prior Workup** | | |
| Group | Statement | Consensus Status |
| Complete Blood Count ( CBC) | Patients should have a complete blood count (CBC) drawn prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| | Patients should have a normal complete blood count (CBC) documented prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| Metabolic Panel [Sodium, Potassium, Chloride, Carbon Dioxide (bicarbonate), Glucose, Total Bilirubin, Total Protein, Blood Urea Nitrogen (BUN), Creatinine, Albumin, Total Protein, Calcium, Magnesium, Potassium] | Patients should have a comprehensive metabolic panel (CMP) drawn prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| Hepatic Function | Patients should have hepatic function tests (alanine transaminase (ALT) aspartate transaminase (AST), alkaline phosphatase (ALP), albumin, total protein, bilirubin, gamma-glutamyltransferase (GGT), lactate dehydrogenase (LD), drawn prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| Urinalysis and Urine studies | Patients should have a urinalysis completed prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| | Patients should have a urine total protein:creatinine ratio completed prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| Other Lab Tests | Patients should have a urine pregnancy test prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| | Patients should have a negative urine pregnancy testing prior to receiving systemic bevacizumab (Avastin) | **Consensus** |
| | Oncology should determine, order, and evaluate all serology prior to the patient receiving systemic bevacizumab (Avastin). | **Consensus** |
| Cardiology/Pulmonology/Radiology Studies: Imaging Studies | Patients should have chest computed tomography (CT) performed prior to receiving systemic bevacizumab (Avastin) | *Near consensus* |
| General Heath History Requirements | Patients should not have a history of major open surgery within 28 days prior to initiating systemic bevacizumab (Avastin) | **Consensus** |

| | | |
|---|---|---|
| | Patients should not have a known hypersensitivity to bevacizumab (Avastin) prior to initiating systemic bevacizumab (Avastin) | **Consensus** |
| | Patients should not have a known upcoming elective surgery scheduled prior to initiating systemic bevacizumab (Avastin) | **Consensus** |
| Recurrent respiratory papillomatosis (RRP)-related symptom | Patients have had multiple episodes of life-threatening airway obstruction prior to starting bevacizumab (Avastin) | *Near consensus* |
| Cardiovascular and Hematologic History | Patients have no history of thrombophilia prior to starting bevacizumab (Avastin) | **Consensus** |
| | Patients have no history of ischemic or hemorrhagic cardiovascular event prior to starting bevacizumab (Avastin) | *Near consensus* |
| | Patients have no history of ischemic or hemorrhagic neurologic event prior to starting bevacizumab (Avastin) | *Near consensus* |
| Airway endoscopic evaluation | Patients have undergone diagnostic microlaryngoscopy and bronchoscopy in the operating room prior to starting systemic bevacizumab (Avastin) | **Consensus** |
| | Patients have undergone microlaryngoscopy, bronchoscopy and biopsy with viral typing in the operating room prior to starting systemic bevacizumab (Avastin) | **Consensus** |
| | Patients have a biopsy excluding malignancy prior to starting systemic bevacizumab (Avastin) | **Consensus** |
| | Patients have undergone microlaryngoscopy and bronchoscopy in the operating room within one month of starting systemic bevacizumab (Avastin) | *Near consensus* |
| Referral/Consulting Service Characteristics | Patients (or parents, if the patient is a child) have consented to off-label use of systemic bevacizumab (Avastin) prior to starting the medication | **Consensus** |
| | Patients have been evaluated by an oncologist prior to starting systemic bevacizumab (Avastin) | **Consensus** |

| **Table 2: Consensus and Near Consensus Statements- Binary (Forced choice)** | | |
|---|---|---|
| **Domain 1. Patient Characteristics** | | |
| Group | Statement | Consensus Status |
| Age at Onset | Age at onset SHOULD NOT be considered when deciding to treat with systemic bevacizumab (Avastin) | **Consensus** |
| Age at Treatment | Age at time of treatment SHOULD NOT be considered prior to the use of systemic bevacizumab (Avastin) | **Consensus** |
| **Domain 4. Prior Treatment Characteristics** | | |
| Group | Statement | Consensus Status |
| Frequency of prior surgical intervention | Frequency of required operative intervention SHOULD be taken into consideration when choosing to administer systemic bevacizumab (Avastin) | **Consensus** |