CASE REPORT

Epidermal growth factor receptor inhibitor therapy for recurrent respiratory papillomatosis [v1; ref status: indexed, http://f1000r.es/1vh]

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Abstract
The epidermal growth factor pathway has been implicated in various tumors, including human papillomavirus (HPV) lesions such as recurrent respiratory papillomatosis (RRP). Due to the presence of epidermal growth factor receptors in RRP, epidermal growth factor receptor (EGFR) inhibitors have been utilized as adjuvant therapy. This case series examines the response to EGFR inhibitors in RRP. Four patients with life-threatening RRP were treated with EGFR inhibitors. Operative frequency and anatomical Derkay scores were calculated prior to, and following EGFR inhibitor treatment via retrospective chart review. The anatomical Derkay score decreased for all four patients after initiation of EGFR inhibitor therapy. In one patient, the operative frequency increased after switching to an intravenous inhibitor after loss of control with an oral inhibitor. In the other patients there was a greater than 20% decrease in operative frequency in one and a more than doubling in the time between procedures in two. This study suggests that EGFR inhibitors are a potential adjuvant therapy in RRP and deserve further study in a larger number of patients.

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Introduction

Recurrent respiratory papillomatosis (RRP) occurs with human papillomavirus (HPV) infection of the respiratory tract epithelium, typically by HPV types 6 and 11. It is the most common benign neoplastic laryngeal disorder in children. RRP has been associated with an increased risk of airway obstruction. Juvenile onset RRP is more severe and results in more intensive therapy. The mainstay of RRP management remains surgical debulking; however, adjuvant therapies are offered in up to a fifth of cases of RRP.

As a result of the low prevalence of RRP, large controlled trials of adjuvant therapies have been limited. Epidermal growth factor receptor (EGFR) inhibitors have been used as an adjuvant therapy due to the presence of EGFR in papillomas. This case series examines the use of EGFR inhibitors in four patients with life-threatening RRP.

Materials and methods

This was an institutional review board (IRB) approved study to examine the response to EGFR inhibitors in RRP. A waiver of informed consent and an IRB waiver of HIPPA authorization were approved by the IRB prior to the advent of the study as the data was anonymised. Those patients with severe RRP, defined as requiring more than four surgical procedures per year with rapid regrowth of papilloma leading to airway compromise, who had been treated with EGFR inhibitors, were identified and their medical charts reviewed. The interval between operations was based upon the physicians’ intraoperative determination of disease burden and was not determined by a specific protocol. Surgical procedures used included carbon dioxide (CO₂) laser and microdebrider or a combination thereof. The operative notes were reviewed to determine a modified Derkay Severity Score, utilizing the anatomical portion of the scoring system, at the time of each surgical debulking. The EGFR inhibitors used, all of which are FDA approved for EGFR expressing malignancies, included erlotinib (Tarceva®), gefitinib (Iressa®), and panitumumab (Vectibix®). Erlotinib (starting dose of 85 mg/m² PO rounded to nearest 12.5 mg) or gefitinib (starting dose of 325 mg/m² PO rounded to nearest 50 mg) were administered daily while panitumumab (starting dose of 150 mg/m² IV) was given immediately following an operation with a minimum of two weeks. An oral medication was initiated first (gefitinib if available or erlotinib if gefitinib was not available). If there was a concern for oral bioavailability or inadequate response to the oral EGFR inhibitor, patients were then transitioned to IV panitumumab. Informed consent was obtained for all patients.

Results

Four patients from 2003 through 2012 met the criteria listed above. Table 1 includes patient demographic and disease-specific information. EGFR expression and associated grade was determined by immunohistochemical analysis prior to initiation of EGFR inhibitor therapy and is also reported in Table 1. The outcome measures for each patient following adjuvant therapy were compared to their own measures prior to therapy; therefore the diversity in regard to age, viral type, and number of operations within the patient group had no effect on outcome.

The outcome data is included in Table 2. Prior to start of adjuvant therapy the Derkay scores of three of the patients were increasing. Following initiation of the EGFR inhibitor therapy, the Derkay score decreased for all four patients. In one patient, the operative frequency actually increased. She was previously well controlled on oral gefitinib but her condition acutely worsened. This prompted a switch to intravenous panitumumab. Contrastingly, in another patient there was a greater than 20% improvement (decrease) in the operative frequency. In the remaining two patients the time interval between procedures more than doubled.

**Patient 1.** A 3 year old female was diagnosed at 6 months of age and was solely managed surgically until 14 months of age. Prior to panitumumab treatment her Derkay score was increasing and she required weekly operations. She had previously received a trial of erlotinib and celecoxib with minimal effect. She had 23 operations prior to starting IV panitumumab at a dose of 200 mg/m².

Following the switch, her operation frequency decreased, with an operation every 26 days and modified Derkay score of 6 on average (Table 2). The patient has undergone 15 IV treatments with some minimal side effects. These have included a skin rash that decreased with ongoing therapy and resolved off therapy, diarrhea limited by probiotic use, an MRSA leg abscess and untreated iron deficiency without anemia that resolved off therapy. During the most recent operation, her airway was free from papillomas and panitumumab treatment was discontinued and the patient has remained free of recurrence off therapy for 12 months.

**Patient 2.** A 6 year old male was diagnosed with RRP at the age of 2. He received nine microdebrider procedures at an outside hospital prior to referral to us for adjuvant therapy. He was first started on erlotinib and celecoxib, which failed to control his disease. The

| Patient No./sex/age | HPV type | EGFR grade | Current adjuvant treatment | Duration of current treatment (months) |
|---------------------|----------|------------|-----------------------------|---------------------------------------|
| 1/F/3               | 6        | 3          | Panitumumab                 | 15 on & 12 off                        |
| 2/M/6               | 6 & 84   | 2–3        | Panitumumab                 | 23                                    |
| 3/F/7               | 11       | 2–3        | Panitumumab                 | 20                                    |
| 4/M/23              | 11       | 3          | Gefitinib                   | 118 on & 2 off                        |

M=Male, F=Female, EGFR=Epidermal Growth Factor Receptor.
Following panitumumab treatment, his operative frequency and Derkay score have decreased (Table 2). Side effects have included increased thirst, nocturnal enuresis, an acneform rash and untreated iron deficiency without anemia. His height has fallen from the 50th to 25th percentile over two years while on panitumumab. The patient began the HPV vaccination series a few months after starting panitumumab. He has also received diindolylmethane (DIM, Bioresponse®) 150 mg 2–3 times daily. Due to a recent improvement in his condition, his surgical interval has been lengthened to approximately twelve weeks.

**Patient 3.** A 7 year old female was diagnosed at 9 months. Shortly thereafter she received a tracheostomy and G-tube at an outside institution due to the extent of the RRP. Her condition continued to worsen and her care was transferred to our institution for adjuvant therapy.

After failure of a short trial of erlotinib (60 mg/m² daily for 1 month followed by 85 mg/m² daily for 1 month) she was managed briefly with interferon alpha 1.5 million units by subcutaneous injection daily prior to initiation of gefitinib at an initial dose of 325 mg. She was managed with gefitinib and surgical debulking for nearly five years. The patient was discovered to be non-compliant once in the past with worsening of her modified Derkay score after which her mother closely monitored gefitinib administration. More recently, her RRP acutely worsened after which it was decided to switch to IV panitumumab at a dose of approximately 150 mg/m² (later increased to 200 mg/m²). The patient had received 69 laser procedures and four requiring combined mechanical and laser debridement prior to panitumumab.

Side effects have included a rash, increased urinary frequency and nocturnal enuresis, and occasional mild fevers with no known source. Her supraglottic disease was so severe that she was only being treated, and thus scored, for tracheal disease. She was also noted to have progressive iron deficiency without anemia that did not respond to oral iron, though it did improve with IV iron sucrose. She has been less than 5th percentile for height but continues to grow. A recent bone age study showed delay. After another period of worsening RRP, panitumumab was increased to 265 mg/m² and DIM was added. Subsequently oral propranolol was added at 3 mg/kg/day divided into three doses per day (TID) without effect after more than a month. Subsequent to this regime, the panitumumab dose was decreased to 200 mg/m² and daily gefitinib (270 mg/m²/day) restarted with no significant change in operative frequency.

**Patient 4.** A 23 year old male was diagnosed at the age of 3 months. His case has been reported in a previous study. 6. The patient’s co-morbidities include interferon-induced nephrotic syndrome with stage III acute renal failure from focal segmental glomerulosclerosis, hypertension and developmental delay. He was born at 28 weeks gestation. He required a tracheostomy as a result of extensive laryngeal stenosis secondary to RRP. The patient was managed with interferon alfa-2a until approximately 8 years of age.

Due to life-threatening airway obstruction 10 years ago, he was started on gefitinib at an initial dose of approximately 400 mg/m²/day divided twice daily because it was thought the patient would not survive. His Derkay score was based upon the trachea and bronchi only as these were the areas being treated due to complete stenosis of the larynx.

Adverse effects have included acne-form rash, dry skin, and minimal diarrhea. He also developed iron deficiency anemia two years ago requiring iron infusions and occasional blood transfusion. An extensive workup has not found a source of blood loss. He continued to receive gefitinib with satisfactory control of his RRP until June 2013 when a trial period of gefitinib was started in conjunction with increased surgical debridement at the family’s request.

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### Table 2. Treatment and outcome data.

| Patient | Previous treatments | Current treatment | Operation frequency (days between procedures)* | Anatomic Derkay score* |
|---------|---------------------|-------------------|---------------------------------------------|----------------------|
|         |                     |                   | Before treatment | After treatment | Before treatment | After treatment |
| 1       | Erlotinib/celecoxib (oral) | Panitumumab (intravenous) | 12 | 26 | 18 | 6 |
| 2       | Erlotinib/celecoxib (oral) | Panitumumab (intravenous) | 14 | 17 | 15 | 10 |
| 3       | Erlotinib (oral), Interferon alfa-2a (subcutaneous), Gefitinib (oral) | Panitumumab (intravenous) | 28 | 16 | 6 | 4 |
| 4       | Interferon alfa-2a (subcutaneous), Tretinoin (oral), Ribavirin (oral and inhaled), Indole-3-carbinol (oral) | Gefitinib (oral) | 7 | 25 | 9 | 5 |

* Data are reported as median.
Discussion

Our interest in EGFR inhibitors stemmed from the benefit observed with the use of gefitinib in a patient with life-threatening RRP (patient 4 above). Three EGFR inhibitors—panitumumab, gefitinib, and erlotinib—have been utilized in these four patients. In our hands, decrease in papilloma severity has been observed only with panitumumab and gefitinib. The lack of response to erlotinib is surprising given that it targets EGFR and there is a prior report of response to erlotinib and celecoxib. Interestingly there is one prior report of the use of intravenous cetuximab, another EGFR inhibitor, in RRP without effect. The use of EGFR inhibitors in the treatment of RRP is off-label. However, due to the EGFR expression in these patients’ papillomas it was hypothesized that EGFR antagonists could offer benefit.

This case series is justifiably limited in scope; it nevertheless suggests that EGFR inhibitors are a potential adjuvant therapy for the treatment of RRP. Beneficial results were observed in all four patients as evidenced by improvement in the Derkay score. In three of the four patients the operative frequency decreased, with the time interval between operations lengthening to twice what was required prior to EGFR inhibitor therapy in two subjects.

None of the patients experienced serious adverse effects from the medications with minimal tolerable adverse events noted. Common side effects of EGFR inhibitors include skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea. Two patients (patients 2 and 3) developed nocturnal enuresis on panitumumab one of which (patient 3) did not have this side effect while on gefitinib. This has not been previously described with panitumumab or other EGFR inhibitors. All patients developed iron deficiency and one severe anemia which has also not been described previously for the use of EGFR inhibitors. A possible mechanism is EGFR inhibition leading to an increase in hepcidin preventing absorption of oral iron.

Various factors could play a role in the response to adjuvant therapy. These may include: the extent of surgical excision, the method used for surgical debulking, the natural course of the disease and the aggressiveness of the virus. None of the patients have a systemic immune deficiency as an explanation for this variability. For these reasons the study of adjuvant therapies in RRP is problematic. Additionally, as with other adjuvant treatments studied for RRP, the number of patients included in this series is very limited. Larger trials comparing the efficacy of EGFR inhibitors with other promising therapies, such as intracelial cidofovir or vorinostat, are needed in order to determine the relative efficacy of these treatments. EGFR inhibitors appear to improve papilloma disease control as an adjunct to surgical therapy—at least in some patients. They do not appear to eradicate papillomas and at the current time the optimal duration of therapy is unknown. The major side effect to date has been skin rash, which has been successfully managed with emollients, sunscreen for sun exposure and selective use of antibiotics for acneform lesions. Although there may be unknown risks from long-term therapy with EGFR inhibitors, our opinion is that the benefits described outweigh the possibility of future unknown risks.

Conclusion

This case series suggests that EGFR inhibitors are a potential adjuvant therapy for the treatment of RRP as evidenced by the improvement in the modified Derkay scores and the general decrease in operative frequency.

Consent

A waiver of informed consent and an IRB waiver of HIPPA authorization were approved by the IRB prior to advent of the study.

Author contributions

JS and BB conceived the study. All authors assisted with the design of the study. MM carried out the research. All authors contributed to the analysis and interpretation of the data. MM prepared the first draft of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Matthew Moldan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests

JS has served as a consultant to Medtronic. All other authors have no competing interests to disclose.

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References

1. Wiatrak B, Derkay CS: Recurrent respiratory papillomatosis: a review. Laryngoscope. 2008; 118(7): 1236–1247. PubMed Abstract | Publisher Full Text

2. Reeves WC, Ruparelia SS, Swanson KI, et al.: National registry for juvenile-onset recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg. 2003; 129(9): 976–982. PubMed Abstract | Publisher Full Text

3. Morgan AH, Zitch RP: Recurrent respiratory papillomatosis in children: a retrospective study of management and complications. Ear Nose Throat J. 1986; 65(9): 19–28. PubMed Abstract

4. Leung R, Hawkes M, Campisi P: Severity of juvenile onset recurrent respiratory papillomatosis is not associated with socioeconomic status in a setting of universal health care. Int J Pediatr Otorhinolaryngol. 2007; 71(6): 965–972. PubMed Abstract | Publisher Full Text

5. Schraff S, Derkay CS, Burke B, et al.: American Society of Pediatric Otolaryngology members' experience with recurrent respiratory papillomatosis and the use of adjuvant therapy. Arch Otolaryngol Head Neck Surg. 2004; 130(9): 1039–1042. PubMed Abstract | Publisher Full Text

6. Bostrom B, Sidman J, Marker S, et al.: Gefitinib therapy for Life-threatening Laryngeal Papillomatosis. Arch Otolaryngol Head Neck Surg. 2005; 131(1): 64–67. PubMed Abstract | Publisher Full Text

7. Derkay CS, Malis DJ, Zalzal G, et al.: A Staging System for Assessing Severity of Disease and Response to Therapy in Recurrent Respiratory Papillomatosis. Laryngoscope. 1998; 108(6): 935–937. PubMed Abstract | Publisher Full Text

8. Lyford-Pike S, Westra WH, Loyo M, et al.: Differential expression of epidermal growth factor receptor in juvenile and adult-onset recurrent respiratory papillomatosis. Histopathology. 2010; 57(5): 768–770. PubMed Abstract | Publisher Full Text

9. Limskkon A, Susanto I, Soo Hoo GW, et al.: Regression of Recurrent Respiratory Papillomatosis with Celecoxib and Erlotinib Combination Therapy. Chest. 2009; 136(3): 924–926. PubMed Abstract | Publisher Full Text

10. Loyo M, Pai SI, Netto GJ, et al.: Aggressive recurrent respiratory papillomatosis in a neonate. Int J Pediatr Otorhinolaryngol. 2008; 72(6): 917–920. PubMed Abstract | Publisher Full Text

11. Goodnough JB, Ramos E, Nemeth E, et al.: Inhibition of hepcidin transcription by growth factors. Hepatology. 2012; 56(1): 291–9. PubMed Abstract | Publisher Full Text | Free Full Text

12. Derkay CS, Volsky PG, Rosen CA, et al.: Current use of intralesional cidofovir for recurrent respiratory papillomatosis. Laryngoscope. 2012; 123(3): 705–712. PubMed Abstract | Publisher Full Text

13. Yuan H, Myers S, Wang J, et al.: Use of Reprogrammed Cells to Identify Therapy for Respiratory Papillomatosis. N Engl J Med. 2012; 367(13): 1220–1227. PubMed Abstract | Publisher Full Text
Referee Responses for Version 1

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Approved: 31 March 2014

Referee Report: 31 March 2014
Juvenile-onset respiratory papillomatosis is often a severe disease, with an extraordinary burden on the quality of life of children and their families. Surgical approaches, especially debulking and, when not avoidable, tracheotomy, remain the mainstay of therapy for this devastating disease. Therefore, the need for adjuvant medical therapies that may allow long-term remission is evident\(^1\)\(^-\)\(^3\). In this sense, the current case series by Moldan and collaborators is worthy of attention. The series also stresses the fact that several medical adjuvant treatments are available but, unfortunately, none has shown conclusive evidence in terms of efficacy.

The authors treated four patients with an off-label indication for EGFR inhibitors, often combining several molecules (antibodies and tyrosine kinase inhibitors) in the same patients. Furthermore, most patients had in the past received other forms of medical therapy (e.g. celecoxib, ribavirin, INF alpha-2A). It is interesting that patients initially treated with erlotinib (patients 1, 2, and 3), when switched to panitumumab responded better in two cases. This is worthy of attention, as the same holds true for the improved results of cetuximab versus erlotinib in the treatment for head and neck cancer\(^4\).

As the authors and Dr. Bauman state, the major difficulty in the choice of a given adjuvant treatment, including EGFR inhibitors, is the lack of readouts for response stratification. As for oropharyngeal cancer, immunohistochemical evidence of EGFR overexpression is not an accurate predictor of treatment responses. The same holds true for every medical adjuvant therapy.

The relatively low incidence of severe RRP makes it difficult to set up proper randomized clinical trials, a problem which may be palliated by multicenter efforts.

As the authors correctly state, their findings must be considered as preliminary data which need further in-depth evaluation before any specific recommendations may be formulated.

As an outlook, it is likely that further understanding of the molecular pathogenesis of HPV-related tumorigenesis is going to lead to the development of new approaches, for example PI3K inhibitors (given the association between HPV and PI3K mutations in cancer)\(^5\).

References
1. Bishai D, Kashima H, Shah K: The cost of juvenile-onset recurrent respiratory papillomatosis. *Arch Otolaryngol Head Neck Surg.*, 2000; 126(8): 935-939 PubMed Abstract | Publisher Full Text
I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

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Approved: 03 December 2013

Referee Report: 03 December 2013

M. Moldan and colleagues report an intriguing, retrospective case series of four patients with severe recurrent respiratory papillomatosis (RRP) treated with epidermal growth factor receptor (EGFR) inhibitors. Two descriptive features, including a numerical increase in the intersurgical interval for three of four cases, and a numerical decrease in anatomic Derkay score in all four, prompted the authors’ conclusion that EGFR inhibitors have a potential adjuvant role in the management of RRP. Inclusion in this report required both severe disease (defined by the authors as requiring at least four debridements per year) and treatment with an EGFR inhibitor. Authors describe neither a systematic process for case identification, nor how many cases were excluded – raising the question of how selective reporting was avoided.

Particular caution is warranted in clinical interpretation of the results, due to the variable natural history of RRP. The average pediatric patient requires approximately 20 lifetime surgical procedures, including airway debridement. However, 19% of patients demonstrate a more aggressive course requiring more than 40 lifetime procedures, and a small percentage of patients will spontaneously remit. Patterns of surgical frequency for individuals with RRP indicate significant fluctuation in intersurgical intervals, independent of adjuvant use. Moreover, the anatomic Derkay score improved in both the cidofovir and placebo groups in a randomized, controlled trial in juvenile RRP. Thus, descriptive improvements in intersurgical interval or Derkay score as noted in this selective, retrospective report must be treated with caution. This case series, along with other anecdotal reports in the literature, may justify a prospective, randomized trial but do not establish EGFR inhibitor therapy as an adjuvant for RRP.

The use of EGFR inhibitor therapy in RRP, including this report, has been justified by the presence of EGFR over-expression in laryngeal papillomas relative to normal laryngeal epithelium. Of note, EGFR
expression by immunohistochemistry has been a disappointing biomarker of response to EGFR inhibitor therapy in cancers of the lung, colon and head and neck – areas where EGFR inhibitors are currently FDA approved\textsuperscript{10-12}. EGFR expression is unlikely to be an appropriate selection factor for patients with RRP to be treated with EGFR inhibitor therapy. Of particular relevance to this question, in head and neck cancer, EGFR expression is lower in cancers driven by human papillomavirus (HPV) than those driven by tobacco and other environmental carcinogens\textsuperscript{13,14}. Nonetheless, HPV appears to deregulate EGFR independent of expression level: in preclinical models, the E6 HPV oncoprotein increases phosphorylation of EGFR, downstream signaling, and internalization of activated receptor forms\textsuperscript{15}. The importance of EGFR inhibitor therapy, if confirmed in prospective, randomized trials in RRP or other HPV-related neoplasms, will likely relate to HPV biology rather than EGFR expression level \textit{per se}.

References
1. Venkatesan NN, Pine HS, Underbrink MP: Recurrent respiratory papillomatosis. \textit{Otolaryngol Clin North Am}. 2012; 45 (3): 671-694 PubMed Abstract | Free Full Text | Publisher Full Text
2. Armstrong LR, Derkay CS, Reeves WC: Initial results from the national registry for juvenile-onset recurrent respiratory papillomatosis. RRP Task Force. \textit{Arch Otolaryngol Head Neck Surg}. 1999; 125 (7): 743-748 PubMed Abstract | Publisher Full Text
3. Larson DA, Derkay CS: Epidemiology of recurrent respiratory papillomatosis. \textit{APMIS}. 2010; 118 (6-7): 450-454 PubMed Abstract | Publisher Full Text
4. Ongkasuwan J, Friedman EM: Juvenile recurrent respiratory papilloma: variable intersurgical intervals. \textit{Laryngoscope}. 2012; 122 (12): 2844-2849 PubMed Abstract | Publisher Full Text
5. McMurray JS, Connor N, Ford CN: Cidofovir efficacy in recurrent respiratory papillomatosis: a randomized, double-blind, placebo-controlled study. \textit{Ann Otol Rhinol Laryngol}. 2008; 117 (7): 477-483 PubMed Abstract
6. Limsukon A, Susanto I, Hoo GW, Dubinett SM, Batra RK: Regression of recurrent respiratory papillomatosis with celecoxib and erlotinib combination therapy. \textit{Chest}. 2009; 136 (3): 924-926 PubMed Abstract | Publisher Full Text
7. Loyo M, Pai SI, Netto GJ, Tunkel DE: Aggressive recurrent respiratory papillomatosis in a neonate. \textit{Int J Pediatr Otorhinolaryngol}. 2008; 72 (6): 917-920 PubMed Abstract | Publisher Full Text
8. Hao Z, Dillard T, Biddinger P, Patel V: Suppression of respiratory papillomatosis with malignant transformation by erlotinib in a kidney transplant recipient. \textit{BMJ Case Rep}. 2013. PubMed Abstract | Publisher Full Text
9. Johnston D, Hall H, DiLorenzo TP, Steinberg BM: Elevation of the epidermal growth factor receptor and dependent signaling in human papillomavirus-infected laryngeal papillomas. \textit{Cancer Res}. 1999; 59 (4): 968-974 PubMed Abstract
10. Licitra L, Mesia R, Rivera F, Remenár E, Hitt R, Erfán J, Rottey S, Kawecki A, Zabolotnyy D, Benasso M, Störlkel S, Senger S, Stroh C, Vermorken JB: Evaluation of EGFR gene copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study. \textit{Ann Oncol}. 2011; 22 (5): 1078-1087 PubMed Abstract | Free Full Text | Publisher Full Text
11. Licitra L, Störlkel S, Kerr KM, Van Cutsem E, Pirker R, Hirsch FR, Vermorken JB, von Heydebreck A, Esser R, Celik I, Ciardiello F: Predictive value of epidermal growth factor receptor expression for first-line chemotherapy plus cetuximab in patients with head and neck and colorectal cancer: analysis of data from the EXTREME and CRYSTAL studies. \textit{Eur J Cancer}. 2013; 49 (6): 1161-1168 PubMed Abstract | Publisher Full Text
12. Shephard FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsch V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A,
Clark G, Santabárbara P, Seymour L, National Cancer Institute of Canada Clinical Trials Group: Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med.* 2005; 353 (2): 123-132 PubMed Abstract | Publisher Full Text

13. Lassen P, Overgaard J, Eriksen JG: Expression of EGFR and HPV-associated p16 in oropharyngeal carcinoma: Correlation and influence on prognosis after radiotherapy in the randomized DAHANCA 5 and 7 trials. *Radiother Oncol.* 2013; 108 (3): 489-494 PubMed Abstract | Publisher Full Text

14. Troy JD, Weissfeld JL, Youk AO, Thomas S, Wang L, Grandis JR: Expression of EGFR, VEGF, and NOTCH1 Suggest Differences in Tumor Angiogenesis in HPV-Positive and HPV-Negative Head and Neck Squamous Cell Carcinoma. *Head Neck Pathol.* 2013; 7 (4): 344-355 PubMed Abstract | Free Full Text | Publisher Full Text

15. Spangle JM, Munger K: The HPV16 E6 oncoprotein causes prolonged receptor protein tyrosine kinase signaling and enhances internalization of phosphorylated receptor species. *PLoS Pathog.* 2013; 9 (3). PubMed Abstract | Free Full Text | Publisher Full Text

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

**Competing Interests:** No competing interests were disclosed.