# Clinical Outcomes in Patients with Recurrent or Metastatic Human Papilloma Virus-positive Head and Neck Cancer

RAJAN P. DANG[1], VALERIE H. LE[1], BRETT A. MILES[2], MARITA S. TENG[2], ERIC M. GENDEN[2], RICHARD L. BAKST[3], VISHAL GUPTA[3], DAVID Y. ZHANG[4], ELIZABETH G. DEMICCO[4], MARSHALL R. POSNER[5] and KRZYSZTOF J. MISIUKIEWICZ[5]

*Departments of [1]Medical Education, [2]Otolaryngology-Head and Neck Surgery, [3]Radiation Oncology, [4]Pathology, and [5]Department of Hematology-Oncology-Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, U.S.A.*

**Abstract.** *Background: There are few data regarding the role of human papilloma virus (HPV) in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Patients and Methods: A retrospective chart review was carried out using our electronic medical record (EPIC) for all patients diagnosed with HPV-positive R/M HNSCC between 2010 and 2014 with minimum of 6 months of follow-up in order to assess progression-free survival (PFS) and overall survival (OS). Results: We assessed 11 patients who underwent a variety of treatments. PFS and OS were 7 and 34+ months, respectively. Four patients (36%) were still alive and disease-free (median OS of 39+ months). Three disease-free patients had been treated with taxane, platinum and 5-fluorouracil as aggressive curative systemic therapy. Another patient treated with TPF was disease-free for 25 months and died of disease at 42 months. Conclusion: Our study demonstrates favorable prognosis for patients with HPV-positive R/M HNSCC and that aggressive systemic treatment can lead to a prolonged disease-free period or possibly cure, even after metastasis.*

Head and neck squamous cell carcinoma (HNSCC) accounts for 3% of all malignancies in the United States, with 60,000 Americans being diagnosed each year and 12,000 dying from this disease (1). While the risk factors most associated with HNSCC are tobacco and alcohol (2), human papilloma virus (HPV) has been established as a major cause of this disease, primarily as oropharyngeal HNSCC involving the tonsils and base of tongue (3, 4). Despite a decreased incidence of tobacco and alcohol-related HNSCC, the incidence of oropharyngeal HNSCC has been increasing since the 1980s, likely due to an epidemic of HPV infection (4). The HPV-16 genotype is the most frequent high-risk subtype identified, although HPV-18, -31, and -33 have also been implicated (3, 5).

The prognostic value and biological implications of HPV status in locally advanced settings are now well-established (6-11). However, there are considerably fewer data regarding the role of HPV in recurrent/metastatic (R/M) HNSCC. The relatively low rate of recurrence in patients with locally advanced HPV-positive disease has led to a small number of HPV-positive patients entering clinical trials for R/M settings; in these studies, patients were not stratified based on HPV status, and consequently HPV-positive patients can only be analyzed retrospectively (6, 9-11). A lack of standardization in HPV testing and reliance on only p16 in retrospective analysis has also led to a significant overestimation of sample sizes, as well as poor quality data that were already too restricted to be practice-changing or to provide any firm conclusions (11-16).

Additionally, there exist minimal data on the responsiveness of HPV-positive R/M HNSCC to aggressive systemic therapy. While HPV-negative R/M HNSCC generally has a poor response to systemic therapy (11, 13), we hypothesize that aggressive systemic therapy, such as that with taxane, platinum and 5-fluorouracil (TPF), can lead to improved progression-free survival (PFS) and overall survival (OS) in patients with HPV-positive R/M HNSCC due to the superior PFS and OS seen in patients with locoregionally advanced HPV-positive HNSCC treated with chemotherapy (9).

In order to contribute to the currently scarce data for this disease, we present our experience of patients diagnosed with HPV-positive R/M HNSCC between 2010 and 2014 that were evaluated by rigorous HPV testing and treated at our Institution.



*Correspondence to:* Rajan P. Dang, BA, 50 E 98 St., New York, NY 10029, U.S.A. Tel: +1 2567971481, e-mail: Rajan.dang@icahn.mssm.edu

*Key Words:* Human papillomavirus, HPV, oropharyngeal cancer, recurrent, metastatic.

## Patients and Methods

We conducted a retrospective chart review using our electronic medical record (EPIC; Madison, WI , USA) for all patients diagnosed with HPV-positive R/M HNSCC between 2010 and 2014. We collected the following data: demographics (age, gender, smoking status), Eastern Oncology Cooperative Group (ECOG) performance status, tumor histological type, initial tumor site and stage, chemotherapy and targeted therapy schedules, surgery, radiation, date of progression, and pattern of treatment failure.

Patients with at least 6 months of follow-up and p16 and HPV positivity, determined by immunohistochemistry, with a 75% cut-off for positive staining, followed by reflex polymerase chain reaction, respectively, were included (17,18).

The longest length of follow-up was 56 months from diagnosis of R/M disease. The PFS was calculated as the amount of time between the beginning of the first treatment following R/M disease and the date of progression (if applicable), and OS as the time between the date of diagnosis of R/M disease and the date of death (if applicable). If the dates of progression or death were not applicable, PFS and OS were calculated using the last date of follow-up.

## Results

*Patients' characteristics*. With a median follow-up of 34+ months from diagnosis of R/M disease, we identified 11 patients, all males (Table I). All patients were p16- and HPV-positive for their primary disease; all eight patients with metastatic disease had biopsy-proven HPV or p16 positivity of at least one metastasis. Nine patients out of 11 (81.9%) were non-smokers. One patient was an active smoker with a 50-pack-year smoking history, and another had a 20-pack-year history and had quit 10 years prior to diagnosis. All patients had an ECOG performance status of 0-1.

Seven patients had primary tonsillar cancer (63.7%), two had base of tongue cancer (18.2%), and two had an unknown primary (18.2%). Initial treatment for patients, prior to development of R/M disease, was variable. Four patients out of 11 (36.4%) had been initially treated with a combination of surgery and adjuvant chemoradiation therapy (CRT) for locally advanced disease. Four patients (36.4%) had been treated initially with definitive CRT alone. Two patients (18.2%) had been treated with induction TPF followed by definitive CRT. One patient (9.1%) had undergone surgery and declined adjuvant treatment despite positive resection margins. The median time after definitive initial therapy until recurrence for the entire study population was 19 months (range=6-77 months). See Table II for details.

The pattern of initial failure was mainly distant and reflects the highly responsive nature of HPV-positive HNSCC and excellent locoregional control. Eight patients (72.8%) developed metastatic disease and three (27.3%) developed locoregional recurrence. Of the eight patients that presented with metastatic recurrent disease, two patients (25%) developed disease oligometastatic to the lung only.

Table I. *Patients' demographics*.

| | |
|---|---|
| Total patients | 11 |
| Mean age (years) | 55.2 |
| Median length of follow-up (months) | 34 |
| Smokers, n (%) | |
| Prior[a] | 1 (9.1%) |
| Current | 1 (9.1%) |
| Primary site, n (%) | |
| Tonsil | 7 (63.7%) |
| Base of tongue | 2 (18.1%) |
| Unknown trimary | 2 (18.1%) |

[a]Quit >5 years before diagnosis.

The remaining six patients developed multiple metastases: three patients had multiple metastases to both lungs only, and three developed metastases to multiple sites, including lungs, liver, colon, bone, and soft tissue of the abdomen in one case each. See Table III for the sites of initial failure.

*Treatments*. First-line treatment for R/M disease was heterogeneous. With 11 patients in total, eight were treated with curative intent. Two out of three patients with locoregional recurrence were treated with surgical resection, five patients with distant metastases (lung, liver, abdominal wall) were treated with metastatectomy, and 1 patient was treated with external beam radiation therapy (XRT) to the chest. Seven out of 11 patients (72.8%) received first-line systemic therapy. Of these, all seven received cytotoxic chemotherapy, and three patients received a combination of chemotherapy and cetuximab (see Table IV for details).

Median PFS and OS were 7 and 34+ months, respectively. Four patients received TPF as a part of their first line therapy for R/M disease, and disease in two of these patients (18.2% or 2/11) had not progressed at the time of writing (PFS of 7+ and 33+ months, respectively). The remaining nine patients (81.9%) received more than one line of treatment: three received one additional line of therapy, two received two additional lines, and for patients received at least three additional lines of therapy (Table V).

Out of the total 11 patients, six (54.6%) are still alive with a median OS of 39 months (range: 10+ to 56+ months), and 5 (45.5%) have died from the progression of their disease. Of those six that were still alive at the time of writing, four (4/11 or 36%) had no evidence of disease and two were alive with disease. Three of these disease-free patients were treated with TPF (taxane, platinum, 5-fluorouracil) as aggressive curative systemic therapy. Another patient treated with TPF was disease-free for 25 months and died of disease at 42 months.

Three patients initially developed locoregional recurrence. One patient refused subsequent definitive therapy and received only two cycles of TPF and XRT to the neck; his

Table II. *Patient history prior to recurrent/metastatic disease.*

| Patient no. | ECOG | Smoking history | Tumor – primary site | Stage | HPV/p16 status | Initial treatment | Time until first recurrence (months) | Site of first recurrence |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | Non-smoker | Tonsil | T2N2bM0 | HPV16+/p16+ | TORS, adjuvant CRT with cetuximab | 6 | R and L Lobes of liver |
| 2 | 1 | Prior[a], 20PY | Floor of mouth/ base of tongue | T4aN2bM0 | HPV16+/p16+ | Resection, adjuvant CRT with cisplatin | 6 | R and L Lungs |
| 3 | 0 | Current[b], 50 PY | Unknown primary | T2N2bM0 | HPV16+/p16+ | TORS, neck dissection, declined adjuvant treatment | 21 | L Neck |
| 4 | 1 | Non-smoker | Tonsil | T2N1M0 | HPV16+/p16+ | Resection, adjuvant CRT with cisplatin | 77 | R Lung |
| 5 | 0 | Non-smoker | Unknown primary | TXN2bM0 | HPV16+/p16+ | Bilateral tonsillectomy, adjuvant hydroxurea, 5FU, CRT with cetuximab | 29 | R Lung |
| 6 | 0 | Non-smoker | Tonsil | T2N2bM0 | HPV16+/p16+ | CRT with cisplatin | 19 | R and L Lung |
| 7 | 0 | Non-smoker | Base of tongue | T2N0M0 | HPV16+/p16+ | CRT with cetuximab | 18 | Base of tongue |
| 8 | 1 | Non-smoker | Tonsil | T1N2bM0 | HPV16+/p16+ | CRT with cisplatin | 8 | L Neck |
| 9 | 0 | Non-smoker | Tonsil | T4N0M0 | HPV16+/p16+ | TPFx3, CRT with carboplatin and taxol | 21 | Abdominal soft tissue |
| 10 | 0 | Non-smoker | Tonsil | Stage IV | HPV16+/p16+ | TPFx3 and CRT with cisplatin | 29 | Lung, bone, colon |
| 11 | 0 | Non-smoker | Tonsil | T3N1M0 | HPV33+/p16+ | CRT with cisplatin | 17 | R and L Lungs |

5FU: 5-Fluorouracil, CRT: chemoradiation, ECOG: Eastern Cooperative Oncology Group performance status, L: left, HPV: human papilloma virus, PFS: progression-free survival, PY: pack-years, R: right, TORS: trans-oral robotic surgery, TPF: taxane, platinum, 5-fluorouracil. [a]Quit 10 years prior to recurrent/metastatic disease. [b]Quit 3 months prior to initial diagnosis.

disease has not progressed after 7 months, although longer follow-up will be necessary to assess his clinical course. The other two patients were treated with surgical resection alone. Neither of these patients was cured of their disease by initial therapy; they progressed locoregionally at 4 and 32 months, respectively.

Among the eight patients that initially developed metastatic disease, two (25%) were disease-free for at least 2 years after diagnosis and treatment of R/M disease; one was disease-free for 25 months, after which disease progressed, and the other remains disease-free after 33 months and is currently alive without evidence of disease. Both patients had pulmonary metastases, and each was treated with metastatectomy followed by adjuvant TPF; one of these patients, in addition to TPF, received concurrent radiation and cetuximab as a part of his adjuvant therapy. One of the eight patients remains alive and disease-free after initial lung metastatectomy, followed by treatment of a second recurrence with TPF and CRT to the mediastinum.

Table III. *Patterns of initial treatment failure.*

| | n (%) |
|---|---|
| Locoregional only | 3 (27.3%) |
| Distant | 8 (72.8%) |
| Lung – single metastasis | 2 (25%) |
| Bilateral Lung – multiple metastases | 4 (50%) |
| Bilateral Liver – multiple metastases | 1 (12.5%) |
| Bone – multiple metastases | 1 (12.5%) |
| Colon – multiple metastases | 1 (12.5%) |
| Soft tissue – single metastasis | 1 (12.5%) |

## Discussion

With a dataset of 11 patients, our study demonstrated a median PFS and OS of 7 and 34+ months, respectively, after diagnosis of R/M disease. All of our patients were positive for a high-risk HPV genotype (either HPV16 or HPV33). Treatment of R/M HPV-positive oropharyngeal HNSCC has been reported retrospectively from major clinical studies, most extensively from the EXTREME and SPECTRUM trials and a combined analysis from the Radiation Therapy Oncology Group [RTOG] 0129 and 0522 trials (Table VI) (11, 13, 14). Generally, patients who are HPV-positive have better clinical outcomes than those who are HPV-negative, however, HPV diagnosis in the SPECTRUM, EXTREME, and RTOG 0522 trials was indirect and its reliability is questionable.

Similar in design, the EXTREME and SPECTRUM trials assessed patients with R/M HNSCC treated with a combination of platinum and 5-fluorouracil with or without cetuximab, and with or without panitumumab, respectively.

Table IV. *Treatment and clinical outcomes for recurrent/metastatic (R/M) disease.*

| Patient no. | Site of initial R/M | First-line treatment | Intent | Pattern of treatment failure | Site of metastasis | PFS (months) | OS (months), status |
|---|---|---|---|---|---|---|---|
| 1 | R and L Lobes of Liver | TPF×4, resection of liver and gallbladder (metastatectomy), carb/5FU/LV | Curative | Distant | R and L Lobes of liver, duodenum | 11 | 26, DOD |
| 2 | R and L Lungs | Carb/5FU | Palliative | Distant | R and L Lungs | 5 | 10, DOD |
| 3 | L Neck | TPF×2, XRT to neck | Curative | N/A | N/A | 7+ | 10+, NED |
| 4 | R Lung | Metastatectomy | Curative | Distant | Mediastinal lymph nodes | 3 | 41+, NED |
| 5 | R Lung | Metastatectomy, cetuximab CRT, TPF×3 | Curative | Distant | R Lung | 25 | 42, DOD |
| 6 | R and L Lungs | Metastatectomy, TPF×3 | Curative | N/A | N/A | 33+ | 34+, NED |
| 7 | Base of tongue | Resection | Curative | Locoregional | N/A | 4 | 56+, AWD |
| 8 | L Neck | Resection | Curative | Locoregional | N/A | 32 | 53+, NED |
| 9 | Abdominal wall | Metastatectomy | Curative | Distant | Abdominal soft tissue | 13 | 15, DOD |
| 10 | Lungs, bone, colon | Cisplatin, cetuximab, everolimus, celecoxib | Palliative | Distant | Bone | 6 | 23, DOD |
| 11 | R and L Lungs | Carboplatin, 5FU, cetuximab | Palliative | Distant | Lungs | 2 | 37+, AWD |

5FU: 5-Fluorouracil, AWD: alive with disease, Carb: carboplatin, CRT: chemoradiation, DOD: died of disease, ED: evidence of disease, L: left, LV: leucovorin, NED: no evidence of disease, OS: overall survival, PFS: progression-free survival, PY: pack-years, R: right, TORS: trans-oral robotic surgery, TPF: taxane, platinum, 5-fluorouracil, XRT: external-beam radiation therapy.

Table V. *Subsequent treatments after disease progression.*

| Patient no. | Subsequent treatments | Curative intent for second-line therapy | PFS for second-line therapy (months) |
|---|---|---|---|
| 1 | Cetuximab + BYL719, pembrolizumab | No | 1 |
| 2 | Docetaxel, whole-brain radiation and resection of brain metastases | No | 3 |
| 3 | N/A | No | N/A |
| 4 | TPF×3, carb/cetuximab CRT | Yes | 37+ |
| 5 | Carb/5FU/LV; LY28001653; XRT; docetaxel | No | 3 |
| 6 | N/A | No | N/A |
| 7 | Resection; RLL lung wedge resection, TPF; left knee metastatectomy, TPF, XRT to knee; ACE-041, lirilumab and nivolumab; left groin node resection, XRT to left groin; left groin node resection, XRT to left groin | Yes | 11 |
| 8 | Resection; platinum, 5FU, cetuximab, motolimod[a] | Yes | 14+ |
| 9 | Carb/5FU/LV, cetuximab; taxotere | No | 2 |
| 10 | PDL1; PolyICLC; ipilumab; pembrolizumab | No | 7 |
| 11 | Taxotere, cetuximab; SRS, Selinexor; azacitidine, cisplatin, XRT | No | 11 |

5FU: 5-Fluorouracil, Carb: carboplatin, LV: leucovorin, PFS: progression-free survival, RLL: right lower lobe, TPF: taxane, platinum, 5-fluorouracil, SRS: stereotactic radiosurgery, XRT: external-beam radiation therapy. [a]This patient was randomized within a clinical trial and it is unknown if the patient received the study drug, motolimod.

We do not know the number of patients that received treatment after progression in the EXTREME study, since there were no approved second-line treatments available for R/M disease at that time. The SPECTRUM trial, that was designed later, allowed patients to receive second-line cetuximab, as well as cytotoxic chemotherapy, RT, and surgery, although the number of HPV-positive patients that received additional lines of treatment is unclear. In contrast, the majority of patients in our study received more than one treatment. Given that we do not know the number of treatments that patients received in the EXTREME and SPECTRUM studies, it is still unknown if favorable

Table VI. *Clinical outcomes for human papilloma virus-positive recurrent/metastatic head and neck squamous cell carcinoma.*

| Study (Ref) | No. of patients | Treatment | Median PFS (experimental arm/ control arm) (months) | Median OS (experimental arm/ control arm) (months) |
|---|---|---|---|---|
| EXTREME (11) | 18 | Platinum and 5FU with or without cetuximab | 5.8/4.3 | 19.4/7.2 |
| SPECTRUM (13) | 99 | Platinum and 5FU with or without panitumumab | 5.6/5.5 | 11/12.6 |
| RTOG 0522 and 0129 (14) | 182 | Heterogeneous* | 8.2 | 31.2 |
| Our retrospective experience | 11 | Heterogeneous | 7 | 34 |

5FU: 5-Fluorouracil, CRT: chemoradiation, OS: overall survival, PFS: progression-free survival, R/M: RTOG: Radiation Therapy Oncology Group. *Including cisplatin and salvage surgery.

outcomes in HPV-positive patients are a result of the number of treatments a patient receives, young age and a lack of comorbidities, performance status, or better response to therapy.

The differences in HPV testing between our study and the EXTREME and SPECTRUM trials may have also contributed to the differences in our data. HPV status in our case series was assessed via p16 testing by immunohistochemistry and HPV testing by rigorous polymerise chain reaction. The SPECTRUM study only tested for p16, for which they used a 10% cutoff (rather than the currently recommended 75%) (19). As a result, some of these patients were potentially not HPV-positive, thereby biasing or compromising the data. Additionally, in both the EXTREME and SPECTRUM trials, patients with non-oropharyngeal HNSCC were included in the total HPV-positive sample. Given that p16 is an unreliable marker in non-oropharyngeal HNSCC (20), as well as the potentially high false-positive rate (due to the significant number of HPV-negative patients and their tendency to experience relapse), many of the patients in this study might have been misclassified.

On the other hand, PFS and OS from our study population were very similar to those presented in a recent combined analysis of the RTOG 0522 and 0129 trials. As with the SPECTRUM study, however, only p16 testing was used to assess for HPV-positivity in RTOG 0522. Although a 70% cutoff was used, and only oropharyngeal HNSCC was assessed, the possibility of data inadvertently including HPV-negative patients should be considered. As mentioned above, there is a high risk of relapse in the HPV-negative population, thus increasing the likelihood of p16-positive HPV-negative patients being included in the study group. Similarly to our study, patients in the RTOG studies were not treated in a uniform fashion after development of R/M disease. There are also minimal data in these studies on the type and use of subsequent palliative chemotherapy and on the rate of metastatectomies, both of which may impact a patient's survival. Finally, the number of these patients treated without curative intent is unknown.

Of importance, the five patients in our study who underwent metastatectomy as first-line treatment for their R/M disease had a prolonged PFS compared to the overall group. Furthermore, two of these five (40%) were disease-free for at least 2 years, and both of these patients had metastases to the lungs and received adjuvant TPF. The other three patients had metastases to the lung, liver, and abdominal wall, respectively; one patient received induction with TPF, followed by resection of the liver and gallbladder and adjuvant carboplatin and 5-fluorouracil, while the other two did not receive any adjuvant treatment. Consequently, adjuvant TPF may potentially prolong PFS in patients undergoing metastatectomy and potentially lead to cure.

Overall, four patients underwent local surgical resection or metastatectomy without adjuvant systemic therapy as first-line treatment for R/M disease, with a median PFS and OS of 8.5 (range=3-32) and 47+ (range=15+–56+) months, respectively. Disease in these patients progressed and each received at least one additional line of therapy. One of these patients received curative second-line systemic therapy with TPF (PFS=37+ months and OS=41+ months), while another received palliative second-line systemic therapy (PFS=2 months and OS=15 months). On the other hand, three patients received adjuvant systemic therapy in addition to surgical resection as their first-line treatment for R/M disease, with a median PFS and OS of 25 (11-33) and 34+ (26-42) months, respectively. Disease in two of these patients has progressed and they received at least one additional line of therapy. Both received palliative second-line systemic therapy (PFS=1 and 3 months; OS=26 and 42 months, respectively). These data show that adding aggressive adjuvant systemic treatment to surgical resection can prolong PFS, and that curative aggressive systemic therapy can lead to a prolonged disease-free period or possibly cure, even after metastasis.

One case may be illustrative of the history of oligometastatic HPV-positive oropharyngeal HNSCC. This non-smoking patient (#4 in Tables II, IV, and V) was initially diagnosed with HPV-positive cancer of the tonsil in 2005. He underwent surgical resection and received adjuvant cisplatin CRT. He remained disease-free until a single lung metastasis measuring 4.3×2.1 cm on positron-emission tomography in 2012 (time to progression=77 months), was resected. Three months later, he was found to have metastases to mediastinal lymph nodes. He then underwent systemic therapy with TPF followed by carboplatin/cetuximab CRT. He remains disease-free with a PFS and OS of 37+ and 41+, respectively, from his second-line curative systemic therapy.

Due to our small sample size, with nine non-smokers and two patients with a history of heavy smoking, our study has an insufficient number of patients for us to assess the role of smoking in HPV-positive R/M HNSCC.

While our case series is smaller than the major clinical studies cited, the HPV testing of our patients was rigorous, and a major point of our study, curative hope with systemic therapy, is supported by the data. Given the scarcity of data regarding HPV-positive R/M HNSCC, we believe that our dataset provides useful information and a guide for thinking about and determining therapy for patients as we find them. As the HPV epidemic continues, many patients treated with CRT will develop metastatic disease and will need treatment.

## Conclusions and Future Directions

Our study provides a small series of well-annotated data that demonstrates a favorable prognosis for patients with HPV-positive R/M HNSCC when compared to historic HPV-negative data. Furthermore our data show that aggressive systemic treatment with curative intent, such as with TPF, can lead to a prolonged disease-free period or possibly cure, even after metastasis. Given that it is unlikely that there will be large, prospective studies on this disease in the near future, clinicians will have to rely on the body of knowledge gained from this and similar retrospective studies. Given the epidemic of HPV, there will be an increasing number of patients with R/M disease. Patients should be stratified in future trials for R/M HNSCC based on HPV status, and standardizing HPV testing across these trials will be essential. HPV-positive patients have a superior survival because they tend to be younger and have a better performance status than patients with HPV-negative HNSCC and because their cancer is more responsive to local and systemic treatments. Currently active immunotherapy trials with HPV stratification may shed further light on the role of immunological agents with HPV-positive R/M HNSCC, although in preliminary reports single-agent immunotherapy appears to have a similar PFS for both HPV-positive and HPV-negative R/M HNSCC (21).

## References


1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin *65(1)*: 5-29, 2015.

2 Sankaranarayanan R, Masuyer E, Swaminathan R, Ferlay J and Whelan S: Head and neck cancer: A global perspective on epidemiology and prognosis. Anticancer Res *18(6B)*: 4779-4786, 1998.

3 Sturgis EM and Ang KK: The epidemic of hpv-associated oropharyngeal cancer is here: Is it time to change our treatment paradigms? J Natl Compr Canc Netw *9(6)*: 665-673, 2011.

4 Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS and Gillison ML: Human papillomavirus and rising oropharyngeal cancer incidence in the united states. J Clin Oncol *29(32)*: 4294-4301, 2011.

5 Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S and Viscidi R: Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst *100(6)*: 407-420, 2008.

6 Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP and Gillison ML: Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med *363(1)*: 24-35, 2010.

7 Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, Solomon B, Choi J, O'Sullivan B, Kenny LM and McArthur GA: Prognostic significance of p16ink4a and human papillomavirus in patients with oropharyngeal cancer treated on trog 02.02 phase iii trial. J Clin Oncol *28(27)*: 4142-4148, 2010.

8 Lorch JH, Goloubeva O, Haddad RI, Cullen K, Sarlis N, Tishler R, Tan M, Fasciano J, Sammartino DE, Posner MR and Group TAXS: Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: Long-term results of the tax 324 randomised phase 3 trial. Lancet Oncol *12(2)*: 153-159, 2011.

9 Posner MR, Lorch JH, Goloubeva O, Tan M, Schumaker LM, Sarlis NJ, Haddad RI and Cullen KJ: Survival and human papillomavirus in oropharynx cancer in tax 324: A subset analysis from an international phase iii trial. Ann Oncol *22(5)*: 1071-1077, 2011.

10 Huang SH, O'Sullivan B, Xu W, Zhao H, Chen DD, Ringash J, Hope A, Razak A, Gilbert R, Irish J, Kim J, Dawson LA, Bayley A, Cho BC, Goldstein D, Gullane P, Yu E, Perez-Ordonez B, Weinreb I and Waldron J: Temporal nodal regression and regional control after primary radiation therapy for n2-n3 head-and-neck cancer stratified by hpv status. Int J Radiat Oncol Biol Phys *87(5)*: 1078-1085, 2013.

11 Vermorken JB, Psyrri A, Mesia R, Peyrade F, Beier F, de Blas B, Celik I and Licitra L: Impact of tumor hpv status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: Retrospective analysis of the phase iii extreme trial. Ann Oncol *25(4)*: 801-807, 2014.

12 Misiukiewicz K, Camille N, Gupta V, Bakst R, Teng M, Miles B, Genden E, Sikora A and Posner M: The role of hpv status in recurrent/metastatic squamous cell carcinoma of the head and neck. Clin Adv Hematol Oncol *12(12)*: 812-819, 2014.

13 Vermorken JB, Stohlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, Foa P, Rottey S, Skladowski K, Tahara M, Pai VR, Faivre S, Blajman CR, Forastiere AA, Stein BN, Oliner KS, Pan Z, Bach BA; SPECTRUM investigators: Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (spectrum): An open-label phase 3 randomised trial. Lancet Oncol *14(8)*: 697-710, 2013.

14 Fakhry C, Zhang Q, Nguyen-Tan PF, Rosenthal D, El-Naggar A, Garden AS, Soulieres D, Trotti A, Avizonis V, Ridge JA, Harris J, Le QT and Gillison M: Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol *32(30)*: 3365-3373, 2014.

15 Huang SH, Perez-Ordonez B, Weinreb I, Hope A, Massey C, Waldron JN, Kim J, Bayley AJ, Cummings B, Cho BC, Ringash J, Dawson LA, Siu LL, Chen E, Irish J, Gullane P, Hui A, Liu FF, Shen X, Xu W and O'Sullivan B: Natural course of distant metastases following radiotherapy or chemoradiotherapy in hpv-related oropharyngeal cancer. Oral Oncol *49(1)*: 79-85, 2013.

16 Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J, Danish H and Neck Cancer G: Hpv-associated p16-expression and response to hypoxic modification of radiotherapy in head and neck cancer. Radiother Oncol *94(1)*: 30-35, 2010.

17 Bonomi M, Abbott RW, Patsias A, Misiukiewicz K, Demicco EG, Zhang D, Kaufman A, Genden EM and Posner M: Role of human papillomavirus and p16 staining in a patient with head and neck cancer presenting with a synchronous lung nodule: A case report and review of the literature. J Clin Oncol *33(3)*: e13-15, 2015.

18 Yarkin F, Chauvin S, Konomi N, Wang W, Mo R, Bauchman G, Diaz A, Burstein D, Szporn A, Hauptman E and Zhang DY: Detection of hpv DNA in cervical specimens collected in cytologic solution by ligation-dependent pcr. Acta Cytol *47(3)*: 450-456, 2003.

19 Mooren JJ, Gultekin SE, Straetmans JM, Haesevoets A, Peutz-Kootstra CJ, Huebbers CU, Dienes HP, Wieland U, Ramaekers FC, Kremer B, Speel EJ and Klussmann JP: P16(ink4a) immunostaining is a strong indicator for high-risk-hpv-associated oropharyngeal carcinomas and dysplasias, but is unreliable to predict low-risk-hpv-infection in head and neck papillomas and laryngeal dysplasias. Int J Cancer *134(9)*: 2108-2117, 2014.

20 Misiukiewicz K, Bonomi M, Demicco E and Posner M: Controversies and role of hpv16 in recurrent/metastatic squamous cell cancers of the head and neck. Ann Oncol *25(8)*: 1667-1668, 2014.

21 Seiwert T, Burtness B, Weiss J, Gluck I, Eder J, Pai S: A phase 1b study of MK-3475 in patients with human papillomavirus (HPV)-associated and nonHPV-associated head and neck (H/N) cancer. 2014 ASCO Annual Meeting, 2014.

*Received February 5, 2016*
*Revised March 23, 2016*
*Accepted March 28, 2016*