Background: Human papilloma virus positive (HPV(+)) oropharyngeal squamous cell carcinoma (OPSCC) has a markedly improved prognosis over HPV(-) tumors; however, current staging parameters do not account for this difference. The primary aims of this study were: 1) design a risk factor based staging system (RFBSS) to reflect the natural history of these tumors, and 2) test our system using a pilot group of patients with OPSCC.

Methods: A literature review was performed to identify statistically significant prognostic factors specific to HPV(+)-OPSCC in multivariate analysis measured by published hazard ratios (HR). HRs were weighted based on confidence intervals and adjusted accordingly. They were then used to calculate expected overall survival (OS) of patients with various clinical risk factors using the formula \( s(t) = s^{(HR1*HR2)} \), where \( s \) = survival and \( t \) = time.

A retrospective chart review was performed on all patients with newly diagnosed OPSCC treated at a tertiary academic institution from 1/1/2009-12/31/2009. All patients had complete HPV testing and smoking data available, and were also staged according to the AJCC 7th edition staging criteria.

Results: Significant prognostic factors for HPV(+)-OPSCC included >10 pack-years (S+) (adjusted HR (aHR) = 1.95), >=N2b status (N2b+) (aHR = 1.99), and T4 status (aHR = 2.62). After calculating expected survival based on clinical risk factors, Stages I-IV were designated based on 3-year survivals of 90, 80, 70 and 60%, respectively. Stage I included T1-2/N0-2a/S- where S- represents <10 pack-years. Stage II included T1-2/N2b+/S-, T1-2/N0-N2a/S+ and T3/N0-2a/S- lesions. Stage III included T1-2/N2b+/S+, T3/N2b+/S+, T3/N2b+/S-, T3/N0-2a/S+, T4a/N2b+/S- or T4a/N0-N2a/S+ lesions and Stage IV included patients with T4a/N2b+/S+, all T4b tumors or patients who were M1 at presentation.

55 patients met inclusion criteria (85% male, 47/55; average age 59 years), 76% (42/55) were HPV in situ hybridization (ISH) positive, 75% (41/55) were p16 positive, and 93% (51/55) were staged pathologically. Average follow up was 36 months (range:2-57). OS for the entire cohort at 1-/3-years was 96%/86%. Based on AJCC staging, 80% (44/55) were Stage IV, 3/55 were Stage III (5%), 1/55 was Stage II (2%), and 7/55 were Stage I (13%). Stage IV OS at 1-/3- years were 95%/80%. There were no deaths in stages I-III in this cohort and no significant difference in OS between stages (p=0.71). Using the RFBSS, 3/52 were Stage IV (6%), 12/52 were Stage III (23%), 27/52 were Stage II (52%) and 10/52 were Stage I (19%). OS rates at 1-/3-years for stages I-III were 100%/87.5%, 100%/96% and 100%/70%, respectively. No deaths were seen among the three patients with RFBSS Stage IV disease. OS was not significantly different across RFBSS groups (p=0.21); however, there was a trend towards decreasing survival with increased stage.

Conclusion: We designed a RFBSS using mathematical derivations of expected survival based on previously studied prognostic factors. This system was used to stage a pilot group of OPSCC patients, and supported a trend towards decreased survival with increasing stage. A larger subset of patients is currently being studied to more rigorously evaluate our proposed RFBSS.
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HPV IS A TRULY INDEPENDENT RISK FACTOR AND PREDICTOR OF SURVIVAL IN OROPHARYNGEAL CANCER, AND IS A NECESSARY ADJUNCT TO THE UICC STAGING SYSTEM IN THIS DISEASE.

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BACKGROUND:

Oropharyngeal squamous cell carcinoma (OPSCC) is a disease of increasing prevalence worldwide, and is associated with human papillomavirus (HPV). It is of note that HPV positivity in OPSCC is associated with improved survival, however to date no studies have determined if this association is independent of other risk factors associated with cancer outcomes. In a recently published meta-analysis (PMID: 22841677), for which the presenting author was a co-author, it was noted that there is an unmet need for studies on survival benefit of HPV-related OPSCC taking gender, nodal metastases, smoking and alcohol into consideration.

METHODS:

A retrospective review was carried out to identify all newly diagnosed OPSCCs in a 12-year period. Over 330 tumours were identified, and detailed clinicopathological annotation of these specimens was carried out, according to the guidelines of the UK National Cancer Intelligence Network. Ethical approval for the study was obtained. Cores from 190 of these tumours were incorporated into tissue microarrays, to facilitate immunohistochemical (IHC) analysis of biomarkers of interest. In addition, RNA and DNA were extracted from a selection of the tumours for more in depth analysis of genes of interest (including TP63 and TP53). Univariate and multivariate analysis of risk factors and survival was carried out, using a Cox proportional hazards analysis model. The primary endpoint of the study was overall survival, with secondary endpoints of recurrence free survival and disease specific survival also analysed.

RESULTS:

46% of the tumour cohort was positive for p16 IHC and/or CISH for HPV DNA. The total analysis time of the study was 348673 days, and the average follow-up time was 2.8 years. The mean time to recurrence in those who had recurrent disease was 2.6 years, and the overall survival for the cohort was 50.3%. It was found that survival was worse in males than females. HPV DNA detected by CISH and/or p16 IHC positivity were conferred a statistically significant survival benefit, both with uni- and multivariate analyses. The best indicator of good prognosis (with multivariate analysis) was WHO performance status, however UICC stage alone (without consideration of HPV status) was not predictive of overall survival outcomes.

CONCLUSIONS:

Multivariate analysis enabled by a large well-annotated cohort of OPSCC patients indicated that p16 and HPV DNA CISH positivity (as markers of HPV infection) are significantly predictive of improved survival, in spite of other potential confounding factors. The UICC staging system for OPSCC is shown to be unreliable without HPV status in this disease, and this highlights the need for the inclusion of HPV determination in routine clinical care of patients with OPSCC.
Background: A recent publication reviewed trends in treatment of patients with advanced stage squamous cell carcinoma of the oropharynx (OPSCC) using the National Cancer Database (NCDB). However, this review only examined up to 2009 when the FDA approved transoral robotic surgery (TORS). We sought to examine if a change occurred in these trends since the approval of TORS and perform a more detailed analysis of surgical trends in all stages and all subsites of OPSCC.

Methods: Using the NCDB, we analyzed 87,830 AJCC stage I-IV patients with OPSCC under specified subsite codes of the oropharynx, tonsil, and base of tongue who underwent treatment between 1998 and 2011. Patients who received chemotherapy or radiation prior to surgery were excluded. Pearson chi-square tests, univariate and multivariate logistic regression models were used to examine national trends in surgical operations.

Results: Patients who met inclusion criteria were 9,103 (10.4%) oropharynx cancers, 42,759 (48.7%) tonsil cancers, and 35,968 (40.9%) base of tongue cancers. The rate of surgery decreased over the study period from 48.5% in 1998 to 38.8% in 2011. The rates of surgical operation differed by origin with 51.3% of tonsil cancers, 29.5% of base of tongue cancers, and 26.7% of oropharynx cancers receiving surgical management over the time period. 74.8% of Stage I patients had surgery compared to 34.2% of Stage IV patients. There was marked regional variation in the rate of operations performed. The highest operative rate, 53.8%, was observed in the West North Central region and the lowest, 34.7% in the West South Central region. 41.3% of White non-Hispanic patients received surgery compared to 26.9% of Black patients. Patients aged <50 years old received more surgical treatment (49.1%) compared to patients aged >=50 years old (37.6%). Patients living in higher income areas with higher high school graduation rates had higher rates of surgical treatment as well (42.1% and 42.5% respectively). There were no distinct operative rate differences between facility types. In the multivariate logistic regression patients were more likely to receive surgical treatment if they were White, non-Hispanic (OR=1.617; 95% CI: 1.525-1.715), lived in the West North Central region (OR=1.649; 95% CI: 1.525-1.783), were aged <50 (OR=1.588 95% CI: 1.527-1.651), had private insurance (OR=1.770 95% CI: 1.651-1.897), with stage I disease (OR=6.153: 95% CI 5.748-6.587). Black patients living in low income areas with low high school graduation rates were less than half as likely to receive surgery compared to White, non-Hispanic patients living in high income areas with higher high school graduation rates (OR=0.441 95% CI: 0.399-0.488).

Conclusion: Despite FDA approval of the advanced surgical technology and minimally invasive approaches to the oropharynx, surgical treatment rates have continued to decrease steadily since 1998. There continues to be a persistent regional variation in the use of surgery. We found that geographic location and socioeconomic factors affected the preferred treatment modality delivered to patients. Further investigation into the factors involved in the decision-making process by region and the patient-specific factors that groups them into prescribed specific treatments is needed.
THE EPIDEMIOLOGY OF HEAD AND NECK SQUAMOUS CELL CARCINOMA IN THE
NETHERLANDS DURING THE ERA OF HPV RELATED OROPHARYNGEAL SQUAMOUS CELL
CARCINOMA. IS THERE REALLY EVIDENCE FOR A CHANGE?

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Head and Neck Oncology and Surgery and 2) Psychosocial Research, Epidemiology and Biostatistics, the
Netherlands Cancer Institute/ Antoni van Le

Purpose

To assess nationwide changes in incidence, clinical and tumor characteristics and overall survival of
squamous cell carcinoma of the oral tongue (OTSCC), other oral cavity (OCSCC), and oropharynx (OPSCC)
over a 20-year period.

Patient and methods

This study comprised all 16,937 patients with primary OCSCC, OTSCC and OPSCC diagnosed from 1989
until 2008 in the Netherlands. We assessed trends in age-standardized incidence and trends of second
cancers using standardized incidence rates (SIR) and absolute excess risks (AER) as well as changes in
sub-site specific overall survival (OS) over time.

Results

From 1989 until 2008, incidence of OTSCC and OPSCC in males (Estimated Annual Percentage Change
(EAPC) 1.2 and 1.9) and incidence of OCSCC, OTSCC and OPSCC (EAPC 2.0, 1.9 and 2.1%) in females
increased significantly. In males increases in incidence were largely restricted to the 50-64 year age
group (EAPC 1.7 and 3.4 for OTSCC and OPSCC, respectively), while in females incidence increased for
most age-groups. The incidence OCSCC and OPSCC of patients aged<50 years decreased. There was no
evidence for changes in the excess risk of metachronous second cancers after OCSCC, OTSCC or OPSCC
between 1989 and 2009. Although survival increased substantially for OPSCC patients (5-year OS of
33.8% in the first period to 43% in the last period, P<0.001) a similar increase in survival was seen for
OTSCC patients and OCSCC cancer patients (5-year OS 45.4% in '89-'93 to 48.7% in '04-'08, P<0.001).

Conclusion

Although incidence of OPSCC did increase since 1989, especially in females similar increases were seen
for OCSCC and OTSCC, in combination with no changes in excess risk of second cancers, this finding is
rather suggestive for a continued role of smoking and alcohol consumption than for a more prominent
role of HPV in OPSCC.
HPV AND NON-HPV RELATED SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX: AN IRISH PERSPECTIVE

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Introduction:

Worldwide, there are an estimated 85,000 new cases of oropharyngeal squamous cell carcinoma (SCC) per year, of which approximately 30% are HPV-related. There also exists a wide geographic variation in tumours of the oropharynx related to HPV, with a reported prevalence of up to 72% of oropharyngeal SCCs in North America compared to 17% in southern Europe. As a distinct clinicopathological subgroup, these tumours confer a better prognosis and can be afforded alternative treatment methods to traditional head and neck SCCs. We present the results of analysis of archival tumour specimens from patients diagnosed with oropharyngeal SCC presenting at two major Irish head and neck centres between 2000 and 2012.

Methods:

A retrospective study of oropharyngeal SCC cases was conducted on patients diagnosed between January 2000 and January 2013 in two major Irish centres. Data was collected on patient demographics, date of diagnosis, subsite of tumour within the oropharynx, risk factors, treatment obtained, presence of synchronous or metachronous tumours and TNM Staging System. DNA was extracted from formalin fixed and paraffin embedded tissue blocks of patients with any diagnosis of primary or second primary oropharyngeal SCC. Genotyping was performed using INNO-LiPA Extra.

Results:

There were 255 cases of oropharyngeal SCC in the time period. Of these tumours, 60% were palatine tonsil or tongue base, 19% were posterior oropharyngeal wall, 17% soft palate and 4% were epiglottic. 40% of tumours demonstrated p16 positivity. Where smoking status was known, 55% were current smokers with average pack years of 43, 21% were ex-smokers and 24% were non-smokers. Analysis revealed HPV positivity of 36%, the vast majority of these being HPV-16.

Conclusion:

HPV prevalence in oropharyngeal SCCs in an Irish population is similar to prevalence in other European countries. This cohort of patients represents an important subgroup, for whom it may be possible to de-intensify therapy. The population may benefit from the introduction of universal HPV vaccination through primary prevention.
Racial and Socioeconomic Factors Impact Survival of Oropharyngeal Cancer Patients Within the National Cancer Database

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Background

Racial and socioeconomic disparities have been noted in head and neck cancer presentation and outcomes. Several recent studies have suggested that these disparities are driven largely by differences in rates of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) between African-Americans and non-Hispanic Whites. The majority of the investigations into disparate outcomes for OPSCC have been single institutional. The purpose of this study is to further elucidate racial and socioeconomic disparities on a population level.

Methods

A retrospective cohort study of OPSCC patients using data from the National Cancer Database (NCDB) was performed. NCDB is a large national cancer registry sponsored by the American College of Surgery Commission on Cancer (ACS-COC). The following predictors were examined for their impact on overall survival: age, race, insurance status, education level, stage, treatment facility type, and treatment. Actuarial survival rates were generated using the Kaplan-Meier method with log-rank methods used to assess significance. Multivariate Cox Regression modeling for those variables with a p<0.001 was used to determine factors associated with survival.

Results

Data were gathered on 171,466 patients and included in the study. Base of tongue and tonsil accounted for 57.6% and 33.2% of the cohort, respectively, and the vast majority of patients were male (73%). Distribution of AJCC stage was as follows: 12.9% stage 1, 12.8% stage 2, 19.9% stage 3, and 52.7% stage 4. The patient population was fairly incongruous from the typical head and neck cancer patient with only 9.3% being African-American and the majority possessing either private or Medicare insurance (85.5%). Additionally, only 34.3% reported an annual income of less than $35,000.

The mean survival time for the entire cohort was 80.6 months. The mean survival for whites was 84 months compared to 52 months for black patients (p<0.001). Those individuals with private or Medicare insurance experienced a significantly improved mean survival time (84 months) when compared to uninsured (66 months) or Medicaid patients (57 months) (p<0.001).

After controlling for all significant factors in a univariate analysis, the multivariate Cox regression analysis demonstrated that African Americans (adjusted HR 1.53 95% CI 1.48 - 1.58, p<0.001), patients with Medicaid (adjusted HR 1.76, 95% CI 1.7 - 1.82, p<0.001), and uninsured patients (adjusted HR 1.73, 95% CI 1.65 - 1.81, p<0.001) all had an increased risk of mortality. Those patients with an annual income of >$35,000 had a 10% decrease in mortality risk (p<0.001).

Conclusions
This population-level assessment demonstrates notable racial and socioeconomic disparities in OPSCC presentation and outcomes. African-Americans, uninsured patients and patients with Medicaid, and those with low income experienced significantly decreased survival. In contrast to previously published series, these data suggest that HPV status may not account for all of the disparate outcomes seen in the OPSCC population. Furthermore, patients with insurance and access to quality care exhibited improved outcomes suggesting possible methods for addressing racial and socioeconomic disparities in head and neck cancer.
THE IMPACT OF NODAL STATUS ON DISEASE SPECIFIC SURVIVAL IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX IS DEPENDENT ON HPV STATUS AND SUBSITE

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Background: Nodal metastases affect the outcome of patients with head and neck cancer. However, the importance of their presence in patients with p16(+) oropharyngeal tumors has been found not to have prognostic significance by some authors. Understanding the influence of nodal metastases in the outcomes of this patient population is necessary because of the current desire to de-intensify treatment. We analyzed a cohort of patients with oropharyngeal cancer that were treated primarily with open surgery and +/- postoperative RT (PORT) only (i.e. chemotherapy naive) at Memorial Sloan Kettering Cancer Center to determine the impact of nodal metastases on Disease Specific Survival (DSS).

Methods: After IRB approval, 300 patients were identified. These underwent surgery +/-PORT between 1985 and 2005. Tissue was available for p16 analysis in 66% patients (n=201) of whom 52% (n=106) were p16(+). There were a total of 33% tonsil, 23% soft palate and 44% base of tongue cancer patients (n=66,46 and 89 respectively). 181 had a neck dissection. Pathological analysis of these specimens showed that 39 patients were pN0 and 142 pN+. Disease specific survival was calculated using the Kaplan Meier method stratifying for p16 status and subsite. Outcomes were compared using the logrank test.

Results: The median age was 58 years (range 27-84). The median follow up was 65 months (1-277). When all patients were analyzed, the presence of positive nodes after neck dissection did not significantly affect 5 yr DSS pN- 83.8% vs pN+ 73.3%, p=0.455. When stratified for p16 status alone, there was no statistically significant difference between pN- 92.3% vs pN+ 84.0%, (p=0.681) in patients with p16(+) tumors. However patients with p16(-) tumors had poorer DSS though this was not statistically significant 5 Yr DSS pN- 76.7% vs pN+ 56.7%(p=0.134). When stratified by subsite alone, tonsil patients who were pN+ had similar DSS to pN- patients (5 Yr DSS pN- 76.2% vs pN+ 85.7%, p=0.530) whereas base of tongue patients had poorer DSS if pN+ ( 5 Yr DSS pN- 93.3% vs pN+ 68.2%, p=0.189) Stratification by both p16 status and subsite was not possible due to small sample sizes.

Conclusion: In our series, the impact of nodal metastases on DSS of patients with oropharyngeal cancer is dependent on p16 status and primary tumor subsite. Oropharyngeal tumors could represent a distinct clinical entity depending on their subsite and HPV status. Thus we propose that the current indications for adjuvant treatment of these could vary and should be reviewed in the setting of a clinical trial.
HEALTH RELATED QUALITY OF LIFE (HRQoL) SCORES FROM HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC) PATIENTS AT 6, 12 AND 12 MONTHS FOLLOWING DIAGNOSIS PREDICT SUBSEQUENT SURVIVAL INDEPENDENT OF HPV STATUS IN A COHORT OF PATIENTS SCHEDULED FOR CURATIVE SURGERY
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Objectives: To evaluate the predictive effect of health-related quality of life (HRQoL) scores on survival in a cohort of head and neck squamous cell carcinoma (HNSCC) patients at 6, 9, 12 and 18 months after primary diagnosis.

Materials and Methods: One hundred and nine consecutive HNSCC patients reported their HRQoL measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) general (C30) and head and neck (H&N35) parts, at the time of diagnosis and at 6, 9, 12 and 18 months after diagnosis. The following HRQoL sum scores were calculated: A sum score of the general QoL/health scores, one score from the general functional indexes, one score from the general symptom indexes and one score from all the H&N specific indexes. All sum scores were dichotomized with the lowest quartile scored as one group. All patients included were younger than 78 years of age, had adequate cognitive functions, and all were scheduled for curative therapy. At the time of diagnosis self-reported amount of smoking and alcohol consumption, as well as socio-demographic information were registered. A complete clinical history, including co-morbidity information, was retrieved from hospital records. New HRQoL scores were not obtained if not curatively aimed treatment could not more be given. HPV status was determined on tumor DNA isolated from formalin fixed paraffin embedded (FFPE) tissue blocks. The patients were included in the period from November 2002 to June 2005. Survival was determined as of December 2013.

Results: In line with previous published results, but now showing the same with HPV adjustment, when obtained at diagnosis all the HRQoL sum scores predicted survival. At six months, the general HRQoL sum score (RR=0.49; CI: 0.23-1.00; p=0.05), the general symptom sum score (RR=1.9; CI: 1.0-3.5; p<0.05) and the HN sum score (RR=2.2; CI: 1.2-3.9; p=0.01) predicted survival. At nine months the general HRQoL (RR=0.4; CI: 0.2-0.8; p<0.01) and the HN sum scores (RR=3.0; CI: 1.5-5.8; p<0.01) predicted survival. At 12 months the general symptom sum score (RR=3.75; CI: 1.8-7.6; p<0.001) predicted survival. At 18 months the HRQoL sum scores did not predict survival. The survival predictions were mostly independent of age, gender and TNM stage of the patients. Being HPV infected or not did not in general interfere with HRQoL score survival predictions.

Conclusion: HRQoL score obtained during treatment and throughout the first year after diagnosis predicted survival in HNSCC patients.
AN HPV-BASED PREDICTIVE MODEL FOR OROPHARYNX CANCER YIELDS MORE ACCURATE PREDICTIONS THAN TNM STAGING SYSTEM.

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Purpose: Due to the established role of the human papillomavirus, the optimal treatment approach for oropharyngeal carcinoma is currently under debate. The purpose of this study was to evaluate the most important determinants of treatment outcome and to develop a multifactorial predictive model that could provide individualized predictions of treatment outcome in oropharyngeal carcinoma patients.

Methods: We analyzed the association between the most common clinico-pathological factors and overall survival and progression free survival in 168 OPSCC patients treated with curative definitive radiotherapy or concurrent chemoradiotherapy in Center 1. The factors evaluated for their prognostic potential were, amongst others, HPV status as determined by means of PCR and p16INK4A immunostaining, smoking and alcohol history, ACE-27 comorbidity score, pre-treatment hemoglobin levels, gender, age, tumor location and TNM classification. Univariate survival analysis and proportional-hazards models were used to compare the risk of death or progressive-disease among patients. Multivariate models were validated in an external dataset of 189 patients treated in Center 2 (also with radiotherapy or concurrent chemoradiotherapy) and compared to the traditional TNM staging system.

Results: The most important predictors of unfavorable outcome were negative HPV-status, moderate to severe comorbidity, T3-T4 classification, N2b - N3 stage, male gender, lower hemoglobin levels and smoking history of more than 40 pack years. Overall survival was significantly better for patients with an HPV-positive OPSCC (5 year survival rate of 82%), compared to patients with an HPV-negative OPSCC (5 year survival rate of 39%; p<0.0001). Prediction of overall survival using the multi-parameter model yielded a C-index of 0.82 (95% CI, 0.76 - 0.88). Validation in an independent external dataset yielded a C-index of 0.73 (95% CI, 0.66 - 0.79). Stratification of model estimated probabilities showed statistically different outcomes for the three proposed risk groups, in both datasets (p < 0.001; Fig 1). For progression free survival, the final model’s C-index was 0.80 (95% CI, 0.76 - 0.88), with a validation C-index of 0.67, (95% CI, 0.59 - 0.74). A comparison on model performance with TNM staging and HPV alone is shown in Table 1.

Conclusion: The developed multivariate model was superior to TNM classification and HPV alone for prediction of overall and progression-free survival in patients with oropharyngeal carcinoma treated with (concurrent chemo-) radiation, and was validated in an external dataset. Using this model we were able to assign patients into clearly distinct risk groups in both cohorts. The individualized predictions provided with this tool could be used to stratify patients for clinical trials. Further improvement in model performance is expected by adding quantitative imaging features (radiomics).
Figure 1. Kaplan-Meier curves of risk group stratification for (a) overall survival and (b) progression-free survival. Nomogram risk group stratifications are shown for the development cohort (left) and for the validation cohort (right). All survival curves are statistically different (log rank test, \( p < 0.0001 \)).
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<td>(CI, 0.61 – 0.72)</td>
<td>(CI, 0.60 – 0.74)</td>
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Confidence intervals were obtained in a bootstrap procedure (n = 100). * indicates whether the multivariate model performance was significantly higher than TNM or HPV (p < 0.0001).