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Multicenter Trial of [^{18}F]fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography Staging of Head and Neck Cancer and Negative Predictive Value and Surgical Impact in the N0 Neck: Results From ACRIN 6685.

Lowe VJ, Duan F, Subramaniam RM, Sicks JD, Romanoff J, Bartel T, Yu JQM, Nussenbaum B, Richmon J, Arnold CD, Cognetti D, Stack BC Jr.

from ***The Journal of Clinical Oncology****, July 2019*

PURPOSE: The objective of this study was to determine the negative predictive value (NPV) of positron emission tomography (PET)/computed tomography (CT) for the clinically N0 neck on the basis of neck dissection.

METHODS: Participants with newly diagnosed, first-time, head and neck squamous cell carcinoma (HNSCC) and at least one clinically N0 neck side for which dissection was planned were included. A total of 287 participants were prospectively enrolled from 23 American College of Radiology Imaging Network-qualified institutions. PET/ CT was compared with findings at neck dissection.

RESULTS: PET/CT scans and pathology findings were available for 270 N0 neck sides from 212 participants. For visual assessment, the NPV specific to the clinical-N0 sides was 0.868

(95% CI, 0.803 to 0.925). For dichotomized maximum standardized uptake value, the NPVs specific to the nodal basins were 0.940 (95% CI, 0.928 to 0.952) and 0.937 (95% CI, 0.925 to 0.949) at prespecified cutoffs of 2.5 and 3.5, respectively. The optimal cutoff maximum standardized uptake value was determined to be 1.8, with an NPV of 0.942 (95% CI, 0.930 to 0.953). The PET/CT-informed surgical treatment plan was changed in 51 of 237 participants (22%) compared with the PET/CT-blinded surgical plan. In 34 participants (14%), this led to planned dissection of additional nodal levels. In 12 participants (5%), this led to fewer planned dissected nodal levels. Negative PET/ CT scans in N0 necks was true negative in 87% and false negative in 13%.

CONCLUSION: [18F]fluorodeoxyglucose-PET/CT has high NPV for the N0 neck in T2 to T4 HNSCC. The surgical treatment plans on the basis of PET/CT findings may be changed in approximately 22% of this group. These findings suggest that [18F]fluorodeoxyglucose-PET/CT may assist the clinician in deciding on the best therapy for the clinically N0 neck in HNSCC. Well-designed clinical trials should be performed to test the outcome of omitting neck dissection by using PET/CT.

Summary

- Prospective nonrandomized multi-center trial of 212 patients (270 necks) investigating the ability of PET/CT to predict nodal status in cT2-4 N0 HNSCC by comparing pre-operative PET/CT to final surgical pathology from the corresponding elective neck dissection.
- Results are notable for a negative predictive value of 0.94 when using SUVmax cutoff and 0.87 using visual interpretation. The false positive rate was 10% despite low SUVmax cutoff (1.8).

Strengths

- First large prospective multi-institutional trial of PET/CT for the N0 neck across multiple HNSCC subsites.
- The study is well designed, likely generalizable, and sets a reference NPV for PET/CT in the N0 neck.

Weaknesses

- T1 cancers are not included in this study despite T1 cancers being the most likely T stage to present with an N0 neck. Considering the occult metastatic rate is likely higher in T2-4 vs T1 cancers, the results of this study may not be applicable to the most commonly encountered clinical scenario (T1N0).
- PET/CTs were read centrally by experienced radiologists with strict criteria. Whether the strong NPV is generalizable to PET/CTs conducted and read outside of high volume academic centers is unknown.
- Pathology was not conducted in a standardiuzed fashion. The true positive rate of nodal involvement, and thus the predictive value of PET/CT, depends on the thoroughness of both the neck dissections and examination of the nodes harvested by pathology. Neither were standardized or adequately reported.

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Systematic review on location and timing of distant progression in human papillomavirus-positive and human papillomavirus-negative oropharyngeal squamous cell carcinomas.

Tiedemann D, Jakobsen KK, von Buchwald C, Grønhøj C.

from **Head & Neck**, March 2019

ABSTRACT: Distant progression (DP) in oropharyngeal squamous cell carcinoma (OPSCC) has significant impact on morbidity and mortality. This study systematically reviewed the literature on studies reporting location and timing of DP after human papillomavirus (HPV)+ or HPV- OPSCCs. PubMed, EMBASE, and the Cochrane Library were systematically searched for studies reporting DP in patients treated with curative intend for an OPSCC. Outcome was site of and time to DP stratified on HPV-status. Seven studies (n = 1564; 77% HPV+) were included in which 313 patients (20%) developed a DP (70% HPV+). The most common site of DP was the lungs (n = 232) regardless of HPV-status. Patients with HPV+ tumors were more prone to dissemination involving multiple sites (risk ratio = 16.49). There was no difference in time to DP when stratified on HPV-status (P = .10). The pattern of but not time to DP was significantly different in patients with OPSCC when stratified on HPV-status

Summary

- The most common site of metastasis for both HPV+ and HPV- oropharyngeal carcinoma was the lungs
- HPV+ tumors were more prone to have multiple sites of distant progression (RR 16.49), with non-regional nodes (intra-abdominal, axial) being more common in HPV+ (RR 4.79)
- Median time to distant progression did not reach statistical difference between HPV+ & HPV- (though median time to progression was in noted to be longer for HPV+ in the 3 included studies)

Strengths

- This investigation is one of the largest available systematic reviews which compares both timing and site of distant progression for HPV+/- oropharyngeal carcinoma
- Clarification of end organ of distant progression was requirement of eligibility criteria

Weaknesses

- Of the 7 studies included in this review, only 3 included data on time to progression
- Age, gender, and HPV status are included but there is no staging table to allow the reader to have a sense of the cohort which is being analyzed
- Only 1 of the 7 studies commented on primary treatment of the patients, noting that of those who developed distant progression, 22% were initially treated non-surgically, and 8% treated surgically

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Multimodality Treatment of Early-Stage Tonsil Cancer.

Roden DF, Schreiber D, Givi B.

*from **Otolaryngology - Head Neck Surgery**, July 2017*

Objective: Compare survival outcomes between unimodality and multimodality treatments for early-stage tonsil squamous cell carcinoma (SCC). Study Design and Setting Review of the National Cancer Database.

Subjects and Methods: Patients were selected if they were <70 years old with clinical stage I-II SCC of the tonsil, as documented in the National Cancer Database from 1998 to 2011. Palliative and nonstandard treatments were excluded. Propensity score matching was performed, controlling for tumor stage, age, race, comorbidity, insurance status, and year of diagnosis. Overall survival (OS) was compared with the Kaplan-Meier method and log-rank test.

Results: We identified 3247 patients. Radiotherapy (RT) was delivered in 1295 patients (39.9%), surgery in 824 (25.4%), and surgery + RT in 1128 (34.7%). Patients treated with surgery + RT had the highest 5-year OS (81.1%), followed by surgery (67.4%) and RT (63.4%; $P < .001$). In a propensity score-matched subpopulation of 2378 patients, the 5-year OS was 78.8% for surgery + RT, 66.7% for surgery, and 64.5% for RT ($P < .001$). Among patients who underwent surgical tonsillectomy plus elective neck dissection and/or adjuvant RT, the 5-year OS was equal ($P = .29$), and all were superior to RT alone ($P < .001$).

Conclusion: Multimodality treatment is associated with the greatest survival in early-stage tonsil cancer. The addition of tonsillectomy to RT confers a 20% increase in survival. The current guidelines might not offer the most effective treatment. An up-front surgical approach, followed by appropriately selected adjuvant therapy, may result in improved survival for early-stage tonsil SCC. These findings merit investigation in a prospective clinical trial

Summary

- Analysis of outcomes of patients with clinical stage I and II tonsil cancer, identified through the National Cancer Database, reveals improved overall survival for those receiving surgery followed by radiation therapy (81.1%) in comparison to surgery (67.4%) or radiation (63.4%) alone.
- For clinical stage I and II cancer of the tonsil, initial therapy with surgery followed by selected adjuvant therapy may result in improved survival.

Strengths

- Large number of subjects included in the study.
- Highly statistically significant differences identified.

Weaknesses

- Possible selection bias for smaller tumors treated with surgery as the initial therapy.
- Unknown HPV status that could account for the differences seen between the treatment groups

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Frameshift events predict anti–PD-1/L1 response in head and neck cancer

Glenn J. Hanna, Patrick Lizotte, Megan Cavanaugh, Frank C. Kuo, Priyanka Shivdasani, Alexander Frieden, Nicole G. Chau, Jonathan D. Schoenfeld, Jochen H. Lorch, Ravindra Uppaluri, Laura E. MacConaill, and Robert I. Haddad

*from **JCI Insight**, February 2018*

Programmed cell death protein 1 (PD-1) inhibitors have efficacy in treating squamous cell carcinoma of the head and neck (SCCHN), but objective response rates are low. PD-1 ligand (PD-L1) expression alone is not considered a robust predictor of response and additional biomarkers are needed. This 3-year observational cohort followed 126 SCCHN patients treated with anti-PD-1/L1 therapy. Prior to treatment, 81 (64%) had targeted massively parallel tumor sequencing. Of these, 42 (52%) underwent fluorescence-activated cell sorting and PD-L1 immunohistochemistry for tumor immunoprofiling. Six (5%) complete responses (CRs) and 11 (9%) partial responses (PRs) were observed. Those treated with prior chemotherapy (98, 78%) versus only surgery and/or radiation had longer overall survival (OS) (10 vs. 3 months, $P = 0.02$). Smokers had a higher total mutational burden (TMB) ($P = 0.01$). Virus-positive patients had a lower higher total mutational burden (TMB) $P < 0.01$) and improved OS ($P = 0.02$). Higher TMB and CD8+ T cell infiltrates predicted anti-PD-1/L1 benefit ($P < 0.01$, $P < 0.01$, respectively) among virus-negative tumors. TIM-3/LAG-3 coexpression with PD-1 was higher on T cells among nonresponders ($P = 0.03$ and 0.02, respectively). Somatic frameshift events in tumor suppressor genes and higher TMB among virus-negative SCCHN tumors predict anti-PD-1/L1 response.

Summary

- This 3-year, single institution, observational cohort which followed 126 HNSCC patients treated with anti-PD-1/L1 therapy, showed comparable response rates (15%) to previously published trials utilizing PD-1 blockade in advanced HNSCC.
- A higher total mutational burden (TMB) correlates with $CD8^+$ T cell abundance and is predictive of anti-PD-1/L1 response and improved outcomes in HPV-negative patients. The median TMB was similar between virus-positive patients regardless of response outcomes.
- Frameshift mutations, particularly in genes with known tumor suppressor function, occurred more frequently in virus-negative responders than non-responders. In responders, these frameshift mutationss typically occurred in patients that otherwise lacked an alternative mutational signature.

Strengths

- Large cohort of HNSCC patients followed prospectively.
- Balanced numbers of HPV+ (40%) and HPV- (60%) tumors including all HNSCC subsites.
- Provides novel insights regarding the genomic determinants of anti-PD-1/L1 therapy response in HNSCC (13-18%) as tumor PD-L1 expression alone does not necessarily determine response.

Weaknesses

- Observational study where patients were treated with various single-agent anti-PD-1/L1 therapies.
- Only 81 patients (64%) including 12 responders had targeted massively parallel tumor sequencing.
- Overall low number of responders (6 CR, 11 PR) limits analysis to determine predictors of checkpoint inhibitor response.

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