LIHNCS - LUGOL'S IODINE IN HEAD AND NECK CANCER SURGERY: A MULTICENTRE, RANDOMISED CONTROLLED TRIAL ASSESSING THE EFFECTIVENESS OF LUGOL'S IODINE TO ASSIST EXCISION OF MODERATE DYSPLASIA, SEVERE DYSPLASIA AND CARCINOMA IN SITU AT MUCOSAL RESECTION MARGINS

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Background

Oral cavity and oropharynx cancer are increasing in incidence worldwide but survival outcomes have not significantly improved over the last three decades. The presence of dysplasia or carcinoma in situ at surgical margins following resection of squamous carcinoma of the mucosal surfaces of the head and neck has been shown to be associated with a higher incidence of local recurrence and reduced survival. While invasive carcinoma in mucosal surfaces can usually be distinguished from adjacent normal mucous membrane, pre-malignant disease is much less readily distinguished at operation. Normal squamous parakeratinised epithelium contains glycogen within the cytosol. The Warburg effect describes the ten-fold increase in cytosol glycolysis which occurs in malignant and premalignant cells. Potassium iodide (Lugol's iodine) can exploit this by producing a chocolate brown stain in the presence of glycogen and saffron yellow where glycogen is absent. The LIHNCS trial is a randomised, controlled trial in which we assess the effectiveness of Lugol's iodine staining in allowing visualisation and excision of cancer margin dysplasia at time of primary surgery.

Methods/Design

All participants underwent primary surgery with curative intent. After completion of baseline assessment participants were randomised into either a standard surgical treatment arm or surgical treatment including Lugol's iodine staining. Randomisation was stratified by surgeon and site. The assessing pathologists were blinded to trial arm and all specimens were re-reported centrally by a single trial pathologist. The primary outcome measure is rate of surface dysplasia, carcinoma in situ or carcinoma at surface mucosal margins in the Lugol's-treated group versus gold standard management control arm. Secondary outcomes include acceptability of the technique, impact of Lugol's stain on need for further treatment (surgery or adjuvant therapy), two year and five year survival, safety of the technique and quality of life changes with EORTC QLQ-30, 35 and MD Anderson Dysphagia Inventory.

Results

We recruited 419 patients in 28 centres in the UK diagnosed with oral cavity or oropharynx squamous cell carcinoma to time and target. Overall screened to recruited rates were >90%. Our initial power calculation required 300 patients to achieve 90% power and the trial recruited all T stage disease. When recruiting successfully we obtained trial steering committee and trial unit guidance to extend the cohort so that 300 T1-T2 cases were recruited as mucosal dysplasia recurrence was felt at that stage to a more significant factor in early stage disease. Here we report primary outcome measure data regarding effectiveness of Lugol's iodine and impact on need for further treatment.

Discussion
We describe the rationale and design of a unique trial in head and neck surgical oncology to which recruitment occurred successfully in 28 centres. Patient and surgeon acceptability were high. We will describe our principle outcomes at the conference.

Trial registration

Current Controlled Trials ISRCTN03712770.
PHASE II PROSPECTIVE TRIAL EVALUATING MOLECULAR ANALYSIS OF SURGICAL MARGINS IN T1-2 ORAL SQUAMOUS CELL CARCINOMA (SCC) FOR DECISION OF POSTOPERATIVE TREATMENT AFTER PATHOLOGICAL COMPLETE RESECTION

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Background: Patients with oral SCC with favorable pathological results have a 5-year local relapse rate of around 15%. Adding adjuvant treatment after surgery in these patients is debated. The aim of this GETTEC prospective study is to test whether analysis of tetranucleotide microsatellite instability in the surgical margins help to select patients who need postoperative treatment.

Methods: Inclusion criteria: untreated oral SCC, T1-2N0 planned for surgical resection of the primary and neck dissection. The surgeon collected surgical margin specimens (mucosa and deep tissues) from the edges of the surgical defect for frozen section and definitive analyses. Eligible patients after pathological analysis (R0, <=2N+, no ECS, <5 perineural invasion) had molecular PCR DNA analysis of tumor looking for microsatellite instability at UT5085 and L17686. Surgical margin DNA was study if the primary tumor was informative (molecular markers distinguish between cancer DNA and normal DNA). Classification of patients and treatments are presented in figure 1. Primary endpoint: local relapse rate. In patients with informative tumor, negative margins and no adjuvant treatment (Group 2A), a one-stage phase II trial was performed to test whether lack of adjuvant treatment could be an acceptable strategy in terms of 5-year local relapse rate: unacceptable rate p0=15%, promising rate p1=5%, alpha error=0.048, power=94%, required number of patients=85. In patients with informative tumor, positive margins and adjuvant treatment (Group 2B), a one-stage phase II trial was performed to test whether adjuvant treatment could be an acceptable strategy in terms of 5-year local relapse rate: unacceptable rate p0=30%, promising rate p1=15%, alpha error=0.19, power=84%, required number of patients=25. The comparison between "Informative" (Group 2) and "Not informative" patients (Group 1) was planned to study the value of an adjuvant therapeutic strategy based on molecular analysis of surgical margins.

Results: 310 patients were included in 27 French centers between 10/2005 and 06/2009. Among the 228 patients considered as eligible after surgery, 216 had tumor/margins available for molecular analysis. Tumor was informative for at least one of the 2 markers in 136 patients (63%). Molecular margins were negative in 106 of them (78%), positive in 23 (17%) and doubtful in 7 (5%). Among the 106 "negative margins" patients, 17 still received adjuvant treatment. These cases were major protocol violations. In order to perform a conservative analysis, they are not included in the main analysis of the Group 2A trial that is based on the 89 patients who did not receive adjuvant treatment. Mean age 58 years, male 72%, oral cavity 92%, T1 45%, N0 92%. Among the 23 "positive margins" patients (Group 2B), 21 received adjuvant treatment (7 radiotherapy, 5 brachytherapy, 9 re-surgery) and 2 refused any additional treatment. The analysis is based on the 23 patients. Mean age 59 years, male 74%, oral cavity 83%, T1 61%, N0 100%. Review of pathological eligibility criteria is ongoing. The final results of the 2 trials and of the local control rates comparison between "Informative" and "Not informative" patients will be available in June 2014. Grant PHRC
Figure 1:

Included patients N=310

Eligible patients after surgery N=228

Eligible patients with available specimens N=216

Patients with NON INFORMATIVE tumor
GROUPE 1 N=98

No adjuvant treatment
N=68

Patients with INFORMATIVE tumor
GROUPE 2 N=136

NEGATIVE margins
GROUPE 2A N=105

No adjuvant treatment
N=89

POSITIVE margins
GROUPE 2B N=23

Adjuvant treatment
N=23
PROGNOSTIC IMPACT OF PERINEURAL AND LYMPHOVASCULAR INVASIONS IN ADVANCED STAGE ORAL CARCINOMA

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Background: Oral squamous cell carcinoma (OSCC) is the sixth most common cancer accounting for over 500,000 new cases annually worldwide. At present, the most important prognostic factors include histological tumor grade, stage, depth of the tumor invasion, and involvement of regional lymph nodes at the time of diagnosis. Unfortunately, more than 50% of all patients have advanced disease at the time of diagnosis and even with the several improvements in treatment strategies, including surgery, radiotherapy and/or chemotherapy, the prognosis of OSCC patients remains largely unsatisfactory, due to risk of loco-regional recurrence and distant metastasis.

Objective: This study aimed to evaluate the prognostic impact of perineural and lymphovascular invasion on survival in OSCC of advanced stage oral tongue and floor of the mouth.

Patients and methods: Data was retrospectively analyzed on 144 patients with OSCC in advanced stage (CS III-IV) of the oral tongue and floor of the mouth treated primarily with surgery. The included patients underwent radical surgery with neck dissection and adjuvant radiotherapy or radiochemotherapy. For all cases clinical and histopathological features of the primary tumor were ascertained. Lymphovascular invasion, perineural invasion, histological grade, pattern of invasion, tumor size, nodal status, and margins were recorded specifically. Twenty-three variables were analysed by univariate analysis to assess their influence on survival.

Results: Overall survival was negatively influenced by six tumor-related factors: Increasing T stage (P = 0.06), more than two clinically positive nodes (P = 0.018), extracapsular spread of lymph node metastasis (P=0.008), perineural invasion (P = 0.003) and lymphovascular invasion (P= 0.029). Recurrence was positively influenced by lymphovascular invasion (P= 0.045), perineural invasion (P = 0.009) and extracapsular spread of lymph node metastasis (P = 0.006).

Conclusion: The presence of lymphovascular and perineural invasion in oral carcinoma surgical specimens has a significant impact on survival outcomes in patients with advanced stage tumors submitted to radical surgery and adjuvant radio/radiochemotherapy.
PROGNOSTIC RELEVANCE OF CIRCULATING AND DISSEMINATED TUMOR CELLS OF PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

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PURPOSE: Current staging methods for squamous cell carcinomas of the oral cavity (OSCC) need to be improved to detect early metastatic spread and clarify the individual need of therapeutic interventions. Since hematogeneous tumor cell dissemination is a key event in tumor progression we assessed the prognostic significance of disseminated tumor cells (DTCs) in bone marrow (BM) and circulating tumor cells (CTCs) in peripheral blood (PB) from OSCC patients.

MATERIALS AND METHODS: From 110 patients with OSCC, tumors were surgically resected (R0) without neoadjuvant therapy. The CellSearchÔ-system was used to enumerate CTCs. BM was aspirated from the iliac crest, and mononuclear cells (MNCs) were enriched by Ficoll density gradient centrifugation. To detect DTCs, MNCs were immunostained with the pan-keratin antibody A45-B/B3. Additionally, BM samples of a subset of 89 OSCC-Patients (intersection of 74 patients to the first test series plus subsequent cases) were immunostained with the pan-keratin antibody A45-B/B3 and a cocktail consisting of the keratin antibodies LDS23/AE1/AE3 respectively. Results were correlated with clinicopathological parameters and clinical outcome such as recurrence and death during follow-up time (mean 916 days, 461 days respectively).

RESULTS: Ten/80 patients (12.5%) harbored CTCs in PB whereas in 18/90 patients (20.0%) DTCs in BM could be detected. Surprisingly, in only two patients (1.8%) CTCs and DTCs were detected simultaneously. Significant correlations could be found regarding CTCs and tumor size (p=0.04), nodal status and DTCs (p=0.02), and distant metastasis with CTCs (p=0.004) and DTCs (p=0.005). Univariate and multivariate analyses revealed that CTCs and DTCs were significant and independent predictors of recurrence-free survival (p<0.001). Even in consideration of a shortened follow-up time a reduced recurrence-free survival was found significant in patients positively tested for DTCs with A45-B/B3 (p=0.0452). For the LDS23/AE1/AE3-Cocktail no significant parameters were found.

CONCLUSION: Both DTCs and CTCs are independent prognostic markers in OSCC patients, predicting relapse with higher sensitivity at various disease stages than routine staging procedures. Bone marrow might be an interesting target organ for future therapeutic interventions.
INTRODUCTION: Nomograms are user-friendly tools with the ability to take into account numerous prognosticators to predict outcomes for an individual patient. These tools can incorporate factors that influence treatment beyond the classic TNM staging system, including variables such as comorbidities, lifestyles, and histopathologic characteristics. The objective of this study was to develop a prognostic tool to be used after primary curative oral cancer surgery for individualized prediction of overall survival (OS), cancer related mortality (CSM), and locoregional recurrence (LRR) based on host and tumor characteristics.

Patients: Previously-untreated patients with biopsy-proven oral cavity squamous cell carcinoma who underwent surgical extirpation between 1985 and 2009 at a tertiary care referral center (n=1617).

Methods: Demographic, host, and tumor characteristics were available from an institutional database and verified via chart abstraction. There were 920 (56.9%) observed deaths, 344 (21.3%) cancer specific deaths and 474 (29.3%) local and/or regional (locoregional) recurrences. The median follow up was 54 months (range 1 - 334 months). 20 patient and tumor variables were investigated. The first 16 variables were applicable to all patients, whereas the remaining 4 variables were only applicable to patients with positive nodal disease. Missing values in the predictors were imputed using MICE method before conducting multivariable regression analysis. Multivariable Cox proportional hazard rates regression (for OS) and competing risks regression (for CSS and LRR) was employed, where restricted cubic splines were used (if applicable) to model continuous variables relaxing the common linearity assumption. Bootstrap was used for internal validation of the nomogram. C-index was calculated to quantify the model discrimination ability. The nomogram predicts outcomes at 1, 3, and 5 years. Comparisons were conducted to test the accuracy of predicting outcomes for node positive patients using the first 16 variables versus all 20 variables.

Results: The variables with the highest predictive value for OS were age, tobacco use, comorbidity score (WUHNCI), tumor size, deep invasion, subsite within the oral cavity, surgical margin status, vascular invasion, perineural invasion, and nodal status (no neck dissection vs neck dissection without positive nodes vs neck dissection with positive nodes). For pN+ patients, details related to positive nodes (the size of the largest positive node, the number of positive nodes, and nodal extra-capsular spread) added predictive value (p=0.020). The OS prediction accuracy (concordance index) for all patients was 72.9%. Additional variables with predictive value for CSM were alcohol use, histologic grade, morphology, and gender. There were no variables with predictive value for LRR that did not also have predictive value for OS or CSM. The CSM and LRR prediction accuracy for all patients was 74.5% and 65.3%, respectively. Prediction of CSM and LRR for pN+ patients was not improved significantly by adding details related to the positive nodes (p=0.872, p=0.210, respectively).

Conclusions: We have developed nomograms that can accurately estimate OS, CSM, and LRR based on specific tumor and host characteristics in patients with oral cancer. Variables related to positive nodes can be added to improve prediction of outcomes for pN+ patients.
THE IMPACT OF PATTERN OF INVASION IN ORAL CAVITY SQUAMOUS CELL CARCINOMA

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Introduction: Invasive patterns of invasion (POI) have been reported to predict worse prognosis in oral cavity squamous cell carcinoma (OCSCC). However, the relationship between POI and other features that also may impact prognosis is less understood. Our aim is to analyze the impact of POI in the context of other prognosticators in OCSCC.

Patients: All previously-untreated patients who had surgery for OCSCC from 2005 through 2012 at a tertiary care cancer center (n=671).

Methods: Demographic, clinical, and outcomes data were extracted from a pre-existing computerized database and verified with chart review. Pathologic features had been recorded synoptically by dedicated head and neck pathologists as routine clinical practice starting in 2009. POI was categorized into broad pushing front and other invasive patterns (islands, diffuse infiltrates, small cell clusters, and single-cell infiltrates). Margin status was defined as negative (tumor >= 5 mm from the resection margin), close (tumor < 5 mm without involvement), and positive (tumor at the resection margin). POI details were available for 329 (49%) patients. Patients without POI information did not differ significantly from the study group who had POI information in regards to baseline patient and tumor characteristics and oncologic outcomes. The relationship between POI and other accepted prognosticators was analyzed using Pearson's x2 test. Overall survival (OS), cancer-specific mortality (CSM), and locoregional recurrence free survival (LRRFS) were analyzed using the Kaplan-Meier method. Multivariate analysis was performed to compare outcomes of interest between patients with invasive POI and patients with non-invasive POI.

Results: The majority of patients (57%) had cancer of the oral tongue. Thirty (9%) patients had broad pushing fronts and 299 (91%) had invasive POI, 85% of which were invasive islands. Floor of mouth cancers had the highest proportion of invasive POI (31/32; 97%) while retromolar cancers had the lowest (9/11; 82%). Invasive POI tumors correlated significantly with close/positive margins (p=0.037), tumor thickness > 4mm (p=0.003), perineural invasion (p=0.002), moderate/poor histologic grade (p<0.001), positive nodal disease (p=0.003), and adjuvant therapy (p=0.001). In addition, patients who had invasive POI were more likely to have had a neck dissection compared to those who did not (p<0.001). Median follow-up was 21 months (range 1-92). On univariate analysis, invasive POI was associated with worse 2 yr LRRFS compared to broad pushing front (71.3% vs. 92.3%; p=0.021) but was not predictive of OS or CSM. On multivariate analysis, POI was not predictive of LRRFS.

Conclusion: Invasive patterns of invasion are highly prevalent in oral cavity squamous cell carcinoma, irrespective of anatomic sub-site. Invasive POI correlates with other negative prognostic factors such as tumor thickness, perineural invasion, histologic grade, lymph node metastases and positive margins of surgical resection, and is not an independent predictor of worse outcomes in OCSCC.
IMPACT OF ORAL PREMALIGNANCY AND ITS SEQUELAE ON QUALITY OF LIFE - VALIDATION OF A HEAD AND NECK PRECANCERS SPECIFIC QUALITY OF LIFE INSTRUMENT (ERNAKULAM QUALITY OF LIFE QUESTIONNAIRE FOR ORAL PREMALIGNANCY, EQOL-OP)

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Background: There lies an indication for higher need for a paradigm application of outcome measures in oral premalignancy patients in India as the high prevalence and chronic development of symptoms in oral premalignancy are responsible for a major social cost. The diagnosis and management of precancers can have a major impact on every aspect of a patient's quality of life. Despite its importance, quality of life (QoL) is rarely a reported outcome in pre-cancer patients. Thus the non-observance to collect quality-of-life information reveals a lack of information among researchers and clinicians about the necessity and relative effective measures available for assessing quality of life in oral premalignancies.

Aim: To develop and validate a QoL instrument for patients with head and neck precancer-related functional status and well-being, Ernakulam Quality of Life questionnaire for Oral Premalignancy, EQoL-OP (Malayalam).

Methods: Ethical clearance for the study was obtained before the study (IEC/24/2013/MBDC). 62 premalignant patients were surveyed for disease specific structured interview to determine the disease specific symptoms. 20 post graduate students and 23 Dental teachers were interviewed for most common premalignant disease specific symptoms. A phone survey of 54 professionals caring for oral premalignant patients located in Kerala Government Hospitals, Health University hospitals/colleges were carried out to assess the most common disease-specific symptoms. Factor analysis was performed to identify the disease specific domains; then the domain specific scores were standardized for component items, domains were assessed for the construct validity on hypothesis and test-retest reliability. Using the structured decision methods and the theory in instrument development, EQoL-OP was developed and evaluated based on the data measuring QoL before and after the treatment. In evaluating its psychometric properties, internal consistency by Cronbach's alpha and test-retest reliability measured by Spearman rank-correlation coefficients were used. The constructed EQoL-OP instrument was then administered to 85 premalignant patients.

Results: Relevant domains identified were Pain (5 items), Mouth opening (7 items), Burning sensation (6 items), Eating (7 items) and Additional concerns (7 items). The internal consistency (Cronbach's alpha) of each of the domains of the scale was more than the 0.80, with the exception of additional concerns domain with 0.75; and test-retest reliability coefficients for all domains were greater than 0.80 (The spearman rank correlation for the EQoL-OP). Construct validity testing indicated that the correlation of the variants for each domain were as hypothesized. The scores differences between pre-treatment and post-treatment for overall scale, pain, mouth opening, eating, burning sensation and additional concerns domains have statistical significance.

Discussion: The main indication of the study was to assess the outcomes of the diagnosis and treatment provided to the premalignant patients. The results indicated that the EQoL-OP is a reliable and valid measure of a QoL instrument for premalignant patients.
Conclusion: To our knowledge the EQoL-OP is first instrument specific to oral premalignancy which is of good validity, reliability and responsiveness, and can be used to assess quality of life for patients with head and neck precancers.
YOUNG AGE AND PROGNOSIS OF SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE: A META-ANALYSIS ON 3,300 PATIENTS

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Background: Squamous Cell Carcinoma of the Oral Tongue (SCCOT) is one of the most common Head and Neck cancer. In literature remarkable inconsistencies among studies on the prognostic role of age, mainly due to heterogeneity of the case studies and small sample sizes, can be found.

Objective: To clarify the prognostic role of the young age at diagnosis (<=45 years) we performed a comprehensive literature search and a meta-analysis of prospective and retrospective studies, considering recurrence and/or survival as study outcome.

Data sources: We performed a literature search using Pubmed and EMBASE to October 2013 ("Tongue Neoplasms"[ MeSH Major Topic] AND (young or younger or older or elderly or age) (Medical Subject Headings). No language or date restriction were applied. Additional papers were retrieved from references of the most relevant articles.

Study selection: We included all articles that were independent and contained the minimum information necessary to estimate the risk, for younger vs older patients, of at least one among the following outcomes evaluated after 5 years of follow-up: local (LR), regional (RR) and distant recurrences (DR), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS).

Results: The literature search provided 2880 papers containing the key words in the title or abstract. We then identified 118 papers worthy of further investigation. Finally 22 studies were included in this meta-analysis (686 and 2,630 patients classified as "young" and "old" respectively). Eighteen studies provided data to estimate the risk of any recurrence for young patients vs older patients, leading to a pooled hazard Ratio (HR) of 1.22 (95% confidence interval [CI], 1.08-1.39). In particular, the younger were at higher risk of LR, HR=1.31 (95% CI: 1.04-1.65) and DR, HR=2.24 (95% CI: 1.03-4.87), while no statistical difference was found in terms of RR, HR=1.16 (0.85-1.58). Ten studies were included in the analysis of 5-year DFS. The pooled HR for younger vs older patients was 1.35 (95% CI, 1.04-1.75). Finally, nineteen and twelve studies were included in the analysis of 5-year OS and DSS respectively. No difference was found, neither by considering mortality for any cause HR=1.08 (95% CI, 0.80-1.46), nor by selecting only the studies which reported data on mortality caused by the disease, HR=1.35 (95% CI, 0.82-2.21).

Conclusion: Patients younger than 45 at diagnosis, are at higher risk of local and distant recurrence than the older patients. Further, their probability of surviving free from disease is significantly lower than the older patients, though this does not reflect a greater risk of long-term mortality.
AN INTERNATIONAL MULTICENTER STUDY OF PRIMARY TUMOR STAGING FOR ORAL CANCER: A PROPOSED MODIFICATION INCORPORATING DEPTH OF INVASION
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Background

The current American Joint Committee on Cancer (AJCC) staging system for oral squamous cell carcinoma (SCC) demonstrates wide prognostic variability within each stage. Since depth of invasion (DOI) of the primary is well established as an independent predictor of recurrence and survival in oral SCC, we hypothesized that modified T staging categories incorporating DOI may improve prognostic discrimination.

Materials and Methods

This international multicenter study included 3,149 patients with oral SCC treated at 11 comprehensive cancer centers worldwide between 1990 and 2011. Patients with histologically confirmed oral SCC undergoing surgical resection of the primary tumor and neck dissection with curative intent were candidates for inclusion. We assessed the impact of DOI on disease-specific survival (DSS) and overall survival (OS) in multivariable Cox proportional hazard models and investigated for institutional heterogeneity using two-stage random effects meta-analyses. Optimal DOI cut-points within each AJCC T category were identified using Akaike's information criterion (AIC) and likelihood ratio tests. Candidate staging systems were developed and evaluated using Harrel's concordance index (C-index), AIC and visual inspection for stratification into distinct prognostic categories, with internal validation using bootstrapping techniques.

Results

Five-year DSS for the cohort was 76.0% with median follow-up of 3.3 years. On multivariable analysis DOI was a significant predictor of DSS (p<0.001), demonstrated no institutional prognostic heterogeneity between institutions (I^2=6.3%; p=0.382) and resulted in improved model fit (lower AIC, p<0.001). Similar results were obtained for overall survival. Optimal cut-points of 5mm in T1 and 10mm in T2-4 category disease were identified and used to develop a modified T staging system that was preferred to the AJCC system on the basis of lower AIC, visual inspection of Kaplan-Meier curves and significant improvement in the bootstrapped C-index (p=0.007).

Conclusion

Our results show that DOI is an independent predictor of survival in oral SCC and provides complementary prognostic information to the AJCC T category. We propose an improved oral cancer T staging system based on incorporation of DOI that should be considered in future versions of the AJCC staging system after external validation.