Accuracy of contrast-enhanced CT and predictive factors for extracapsular spread in Unknown Primary Head and Neck Squamous Cell Cancer

Introduction

Pathologically proven extracapsular spread (ECS) in node-positive head and neck squamous cell carcinoma (HNSCC) is associated with increased rates of locoregional recurrence, distant metastasis and decreased rates of overall survival. It is found in up to 50% of neck dissections in clinically and radiologically node-positive necks [1]. Its prognostic value may be modulated based on subsite and p16/high risk HPV (HR-HPV) positivity. In the post-operative period when ECS is histologically confirmed, adjuvant chemoradiotherapy has been shown to improve overall survival compared to radiotherapy alone[2]. Ideally, if it was identified at the pre-treatment stage it would allow appropriate counselling and therapy planning. When there is probable ECS on initial staging, it may be preferable to proceed to radical chemoradiotherapy rather than primary surgery. This avoids the increased morbidity of tri-modality management.

The range of sensitivities and specificities for cross-sectional imaging in predicting ECS is 43-80 % and 54-98% respectively. The cohort most commonly studied is oral cavity squamous cell cancer (SCC) patients in whom surgical staging is more commonly performed and where neck dissection histology is therefore readily available for analysis. Necrosis on imaging is one of the more commonly noted predictors of ECS[3-5]. Other radiological features such as irregular nodal borders, perinodal fat stranding, size, loss of fat planes and adjacent structure invasion have also been explored. Radiographically determined ECS is an

independent prognosticator of poor distant disease control and survival in locally advanced oropharyngeal SCC[6] although Maxwell et. al. and Chai et. al. concluded that CECT was not reliable for ECS prediction in a p16 positive and mixed cohort of HNSCC patients respectively[7,8].

Disease presentation with a metastatic cervical node is relatively common in HNSCC and the primary mucosal site is often detected during subsequent workup. However, around 2-9% of patients exhibiting neck lymph node metastasis from HNSCC have an occult primary cancer[9], that is, no primary site is identified despite extensive diagnostic scrutiny. The investigative pathway includes clinical examination, CT scan +/- MRI scan and PET-CT scan, examination under anaesthetic (EUA), tonsillectomy and targeted biopsies of potential primary sites. In unknown primary cancer, there is no primary tumour "T" stage or surgical margins to help with prognostication and treatment planning and detection of ECS, a known independent prognostic factor for survival in these patients,[10] is crucial for management.

The aim of this study was to assess the accuracy of contrast-enhanced CT (CECT) at predicting ECS and to determine what imaging and clinicopathological features are associated with ECS in an UPHNSCC cohort.

Materials and Methods

Study Population

33 patients were identified with true UPHNSCC – negative primary sites on CT/MRI, PET/CT, EUA, tonsillectomy and biopsies. These patients underwent comprehensive neck dissection as their primary treatment and were retrospectively identified from a central MDT database between January 2011 and December 2015. 2 patients were excluded as they had not had a contrast-enhanced CT performed pre-operatively within 10 weeks of surgery. All had unilateral neck disease. The following information was recorded: demographics, clinicopathological details including HPV status, pathological nodal stage, (UICC TNM 7th edition applied in this time period), whether core biopsy performed and adjuvant therapy.

CT Examinations

Contrast enhanced CT of the neck was performed across 6 institutions on 12 CT scanners. Scanning at these sites was performed with 125 ml of IV contrast medium (Omnipaque 300 (GE Healthcare)) injected as a split bolus: typically 75 ml at 2 ml/sec followed by 50 ml at 2 ml/sec and the neck scanned with arms down at 100 secs after the start of injection. Images were obtained with between 16 and 128 detectors at 120 kVp, 50-300 mAs, with rotation time of 0.5-0.75 secs, pitch of 0.67-0.83 and slice width of 0.5-1.25 mm. All images were retrieved using the commercially available picture archive communication system (Carestream PACS (Rochester NY)) and evaluated at 3 mm thickness using multiplanar reconstructions.

Following creation of an anonymous patient list on PACS, two head and neck consultant radiologists (“A and B”) with 5 and 15 years experience, reviewed each CT scan without

prior knowledge of histopathology findings, original radiology report or adjuvant treatment. Each observer made an independent blinded dichotomous assessment regarding presence or absence of ECS in the largest radiologically involved node at each diseased nodal level (I-V). Assessment was done by nodal level to match the resolution of histology reports. Subsequently, in consensus, these nodes were assessed for the following: largest diameter in any plane, loss of sharp margin - edge of the node being indistinct at any point (Figure 1), haziness in adjacent fat - stranding and increased density in the surrounding adipose tissue (Figure 2), internal necrosis as evidenced by central low density and loss of fat plane with adjacent structures such as sternocleidomastoid muscle.

Statistical analysis

Accuracy of independent binary assessment for presence or absence of ECS was assessed at the nodal level with interobserver agreement determined with weighted kappa. Fisher's exact test and unpaired student's t test were utilised where appropriate, to compare the imaging and clinicopathological findings and presence of histological ECS using the largest involved node per patient. Logistic regression was then performed to determine independent predictors of ECS and to quantify the effect sizes. All analyses were done using Minitab (version 18) at a 5% significance level.

Ethical considerations

Research ethics committee advice was sought using the online tool from the NHS health research authority and Medical Research council website and was not required[11].

Results

Patient details

Of 31 patients, 23 were male, and 8 female, with mean age 58 years (SD 8 years, range 41-69 years). CECT was performed at a mean of 40 days (SD 13 days, range 13-68 days) prior to neck dissection. Nine patients had high-risk HPV (HPV 16) identified using in-situ hybridisation, nine were HR-HPV negative while 13 did not have p16 status or HPV status assessed at the time of the analysis. 24 patients had undergone core biopsy of one of the involved nodes for tissue diagnosis, the remainder were diagnosed with fine needle aspiration (FNA). Nineteen patients had adjuvant chemoradiotherapy and 6 had radiotherapy alone.

Reader Results

39 cervical node levels contained pathological looking nodes on CECT. ECS was suspected in 29 and 27 levels by observer 1 and 2 respectively. Histopathological ECS was confirmed in 26 levels in 23 patients. This involved level I (1), level II (17), level III (7), level IV (0) and level V (1). The sensitivity of subjective assessment for ECS by nodal level was 81-85% (CI 65-93%) and specificity 46-54% (CI 19-81%). Positive predictive value was 76-78% and negative predictive value 58-60%. There was excellent inter-rater agreement (kappa=0.874).

Univariate analysis

On univariate analysis, based on the largest abnormal node per patient, haziness in the adjacent fat (p 0.02) and longest nodal dimension $\geq$30mm (p 0.01) were statistically significant radiological features predictive of ECS, while patient age (p 0.006) and

pathological nodal status (N2/3 versus N1) (p 0.002) were statistically significant clinicopathological findings. (Table 1)

Loss of sharp margin, nodal necrosis, loss of fat plane with adjacent structures, sex of the patient or preceding core biopsy of an involved node showed no statistically significant relationship with ECS.

Multivariate analysis

On multivariate analysis, haziness in the adjacent fat showed an increased risk of ECS, with an odds ratio (OR) of 26.4 (1.2-594) as did increasing age of the patient with an odds ratio of 1.24 (1-1.5) (table 2), that is an OR of 1.24 for each year older a patient is. The OR for haziness in the adjacent fat has a very wide confidence interval due to the small sample size: only 1 of 14 patients with haziness did not have ECS.

Discussion

The aim of this study was to assess the accuracy of contrast-enhanced CT (CECT) to detect ECS and determine which radiological and clinicopathological features were most predictive of this in patients with head and neck cancer of unknown primary. This analysis contains a novel and homogenous cohort of patients, where extracapsular spread is known to be a significant predictor of survival. This study demonstrates that nodal longest diameter ≥30mm, haziness in the surrounding fat on pre-operative CECT, increasing age and more advanced pathological nodal stage were statistically significant predictors of ECS. This is the first paper to demonstrate these findings in this patient subdivision.

UPHNSCC and ECS

Head and neck squamous cell cancer of true unknown primary represents only 2-9% of all head and neck cancers[9]. This is a fairly unique group of patients in whom there is neither T stage of the primary tumour nor resection margin information to direct treatment and predict outcome. There are no randomised controlled trials assessing the optimal management of UPHNSCC, therefore there is no standard treatment model. Guidelines suggest the approach should be curative with the least morbidity to the upper aerodigestive tract as possible. This could be single or combined modality treatment depending on the extent of the disease. The addition of chemotherapy to adjuvant radiotherapy should be considered in N1 disease and above, if there is ECS. The escalation of treatment to tri-modality in patients with ECS has potentially significant treatment morbidity without necessarily improved outcomes compared to chemoradiation alone therefore detection of ECS pre-treatment can help guide management decisions.

Imaging features and ECS

In this cohort, haziness in the fat around the involved node was a highly significant predictor of ECS (OR 26.4). This increased density and stranding in the surrounding low density fat, which can range from subtle to marked, presumably relates to macroscopic extranodal spread of disease. Aiken et. al. found perinodal stranding to be marginally statistically significant for ECS with p 0.055[3]. Furthermore, maximum diameter as assessed on CECT ≥ 30mm was also significantly associated with ECS. The strong association between ECS and size (assessed clinically) was first reported over 30 years ago by Carter et al who reported that nodal masses greater than 3 cm were more likely to have "trans-capsular" spread[12]. Reviewing comparable literature, several findings have been shown to help predict ECS radiologically, with mixed groups of patients (Table 3). These are predominantly from studies of oral cavity SCC. One of the difficulties with heterogenous series is that there is wide biological modulation between different head and neck subsites. HPV-positive oropharyngeal cancer contrasts with HPV-negative carcinoma of the larynx, for example.

The most common predictor of ECS in previously published papers has been central node necrosis yet this current series did not demonstrate this. Both Randall et al and Aiken et. al. found that central nodal necrosis was an independent predictor of ECS, however only oral cavity SCC patients were studied [3,4]. A consideration is the prevalence of high risk-HPV positivity in patients with UPHNSCC, reported as ranging from 22-52%[13] and the fact that cystic nodes are particularly recognised with HPV-related head and neck squamous cancers. An earlier study established strong association with HPV tonsillar cancer and cystic cervical nodal metastases[14]. HPV data for this cohort is incomplete but contains 50% of patients with HR-HPV positive SCC. Our criteria for nodal necrosis on CECT was the presence of central

fluidic density. It is quite feasible that there is overlap between truly cystic and genuinely necrotic nodes on imaging, which is a histopathological distinction. CT has limited ability to distinguish internal necrotic debris from cystic change and HPV-related cystic nodes are potentially more represented here compared to an oral cavity SCC group.

Our sensitivity is higher than many reported series although specificity is lower. Awareness of the previously published findings in relation to perceived necrosis may have skewed the decision of both observers to denote ECS positivity with all but 2 levels having central low/fluid density in the relevant node, theoretically increasing false positives and diminishing specificity.

Combining several imaging parameters for example $\geq$3 cm and haziness in the fat in ECS prediction could improve the specificity but at the possible expense of sensitivity. MRI and PET-CT have similarly been explored in relation to predicting ECS. MRI has reported sensitivities of 50-80% and specificities of 85-100% depending on the imaging parameters used[15,16] while predictive values of SUV max on PET/CT have shown conflicting results[17,18].

Currently, contrast-enhanced CT scanning is the most efficient and effective diagnostic modality for ECS assessment. A large study of 508 patients[19] observed that CT had higher accuracy versus MRI for extranodal extension at 80% vs 68% although this was not statistically significant. Interestingly, in their study when the imaging to surgery interval was >8 weeks the accuracy of scanning overall fell from 73% to 48%.

Clinical features and ECS

Increasing age was a predictive factor for ECS in this series, a new finding in UPHNSCC. HNSCC most commonly presents in the seventh decade and increasing age has been shown

to be a relevant prognostic factor for overall survival. Halmos et al demonstrated that older patients (>80 yrs) are less likely to receive tri-modality treatment and in our practice, patients over the age of 70 do not currently receive chemotherapy due to the lack of evidence to support improved survival. They are overall more likely to be managed with palliative intent for which ECS may be taken into account when making such a decision at the MDT[20].

Pathology features and ECS

The nodal status of any head and neck cancer is a significant predictor for disease specific and overall survival including UPHNSCC. We demonstrated, as expected, that pN2/3 was significantly more likely to predict ECS compared to N1. Nodal status has frequently been shown to be a reliable predictor of ECS and therefore this parameter has the potential to guide treatment decisions. However pathological nodal status is of course only available post-operatively.

TNM

Such is the importance of ECS in prognosis, the AJCC/UICC TNM 8th edition has incorporated clinical evidence of extranodal extension (ENE) into the staging of p16-negative oropharyngeal and hypopharyngeal SCC patients. However, a high bar for inclusion is recommended[22] and stage migration must be avoided if possible with ECS not over-called radiologically. Since the introduction of TNM 8th edition, our practice is to report ECS and make note of it in the MDT setting. This can guide treatment decisions but correlation with clinical findings is advised prior to formally upstaging p16 negative oropharyngeal and hypopharyngeal SCC patients.

Limitations

Published series report low intra and inter observer agreement on the assessment of pathological ECS[24] and indeed there is no internationally agreed standardisation, which has been called for[25]. This would greatly improve comparison between studies.

Potential weaknesses of this multicentre study include the small sample size however UPHNSCC represents a minority of head and neck cancers making it difficult to analyse a large sample size of this patient subset. Nonetheless it is a novel cohort. It could be of value to perform a similarly designed larger study in oral cavity SCC where the findings could be extrapolated to p16 negative oropharyngeal SCC where ECS is considered of more prognostic significance.

We do not have complete p16 or HR-HPV PCR data as at the time of diagnosis as this was not routinely tested in the early years of this dataset, although this is now done consistently in oropharyngeal and unknown primary HNSCC in line with the national head and neck cancer guidelines published in 2016[26].

CECT was performed on a large range of scanners across a number of institutions. Despite this, a standardised protocol was applied, all scans were deemed diagnostically adequate and were able to be viewed in multiplanar reformat and this variability may increase the applicability of the findings to a wider group of UPHNSCC patients.

We did not differentiate between microscopic and macroscopic ECS nor was the degree of ECS graded by severity histologically, rather a dichotomous outcome was determined from the pathology report summary. Regardless, our sensitivity was high and this would not have

improved our specificity. The assessment of individual imaging parameters was done in consensus rather than individually as we felt this more reflected what is done in day to day practice and during MDT preparation.

Conclusion

This study demonstrates some novel findings for the prediction of extracapsular nodal spread in an unknown primary HNSCC cohort. The sensitivity was 81-85% although specificity was 46-54%. Interrater agreement was excellent. Nodal largest diameter ≥ 30 mm and increased pN status correlated with ECS. Haziness in the adjacent fat and increasing patient age were statistically significantly associated with ECS on both univariate and multivariate analysis. Results are at variance with other published findings. This may reflect the cohort being observed, but also highlights the need for ongoing further larger studies. Radiological assessment for suspected ECS is beneficial for clinical decision making and valuable for prognostication and treatment planning, particularly in the unknown primary group where other parameters such as T stage and surgical margins are unavailable. Notwithstanding, care must be taken to avoid inappropriate stage migration in p16-negative oropharyngeal and hypopharyngeal SCC patients and escalation to multimodality therapy must be justifiable.

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349 Table 1. Univariate analysis.

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	ECS positive **N=23**	**ECS negative** **N=8**	**p value**
Size LD ≥30 mm	**18 (78%)**	**2 (25%)**	**0.007**
Loss of sharp margin	19 (83%)	4 (50%)	0.080
Haziness in fat	13 (57%)	1 (13%)	0.023
Necrosis	22 (96%)	8 (100%)	1.000
Loss of fat plane	23 (100%)	7 (86%)	0.258
Age (yrs) Mean (SD)	60 (7)	51 (7)	0.006
Male	17 (74%)	6 (75%)	1.000
pN2/3 (vs pN1)	22 (96%)	3 (38%)	0.002
Core biopsy	17 (74%)	7 (86%)	0.642

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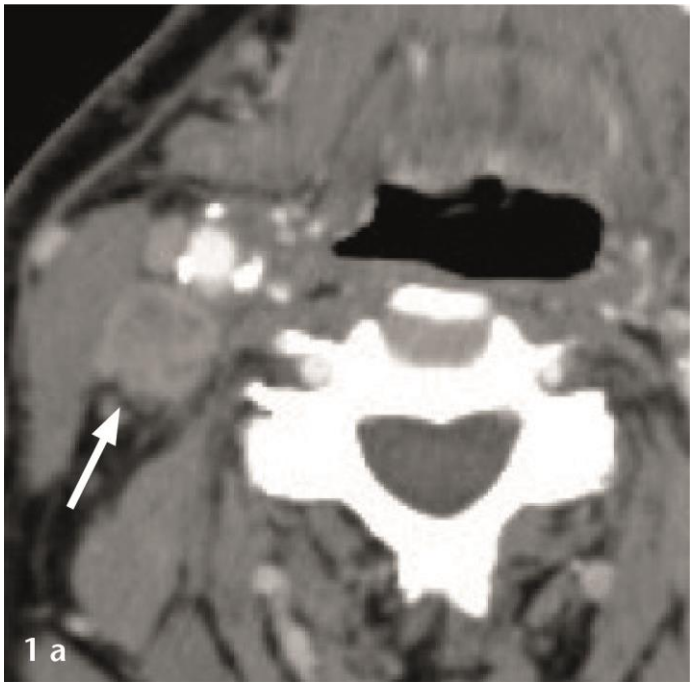
Table 2. Multivariate analysis.

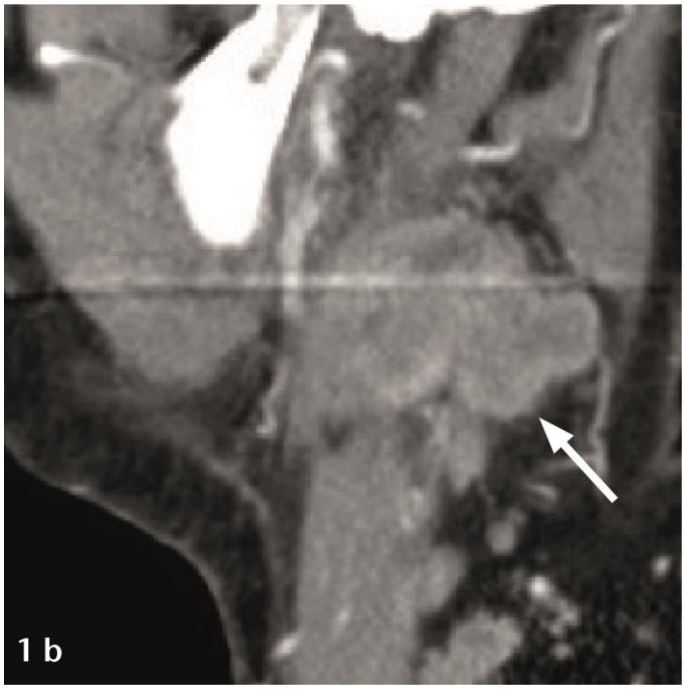
Variable	p value	Odds ratio
Age	0.002	1.24 (1-1.5)
Haziness in Fat	0.009	26.4 (1.2-594)

Figure Legends

Figure 1 Axial (a) and Sagittal (b) contrast enhanced CT scan demonstrating loss of sharp margins – arrows.

Figure 2. axial (a) and sagittal (b) contrast enhanced CT scan demonstrating haziness in the adjacent fat – arrows





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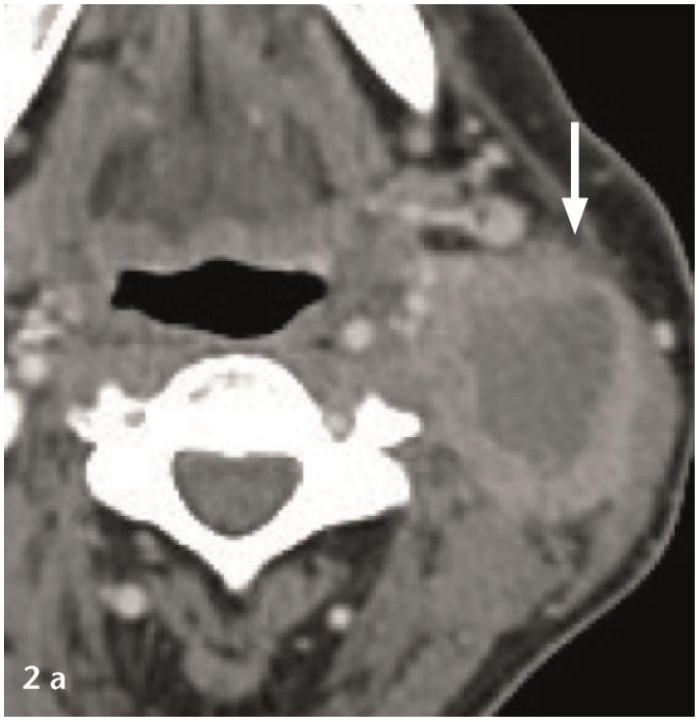

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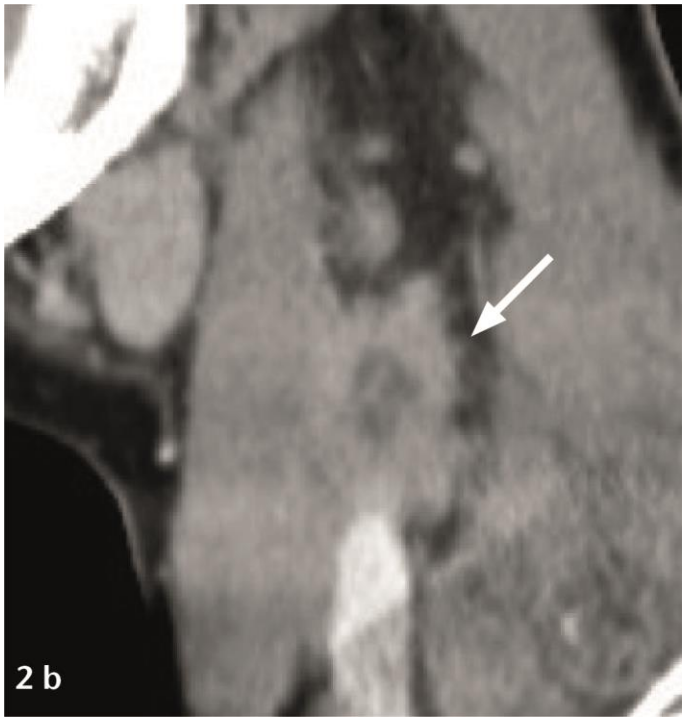
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