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The Christie score for post-treatment response assessment PET/CT in patients with head and neck squamous cell carcinoma: a safe and simple scoring system

N. Baguley[1*], C. Barker[2], S. Bonington[2], S. Mak[2], A. Chander[2], J. Price[2], A. Datta[2], R. Nadir[2] and G. Betts[3]

*Correspondence:
nathan.baguley@nhs.net

[1] Radiology Department, The Christie NHS Foundation Trust, Wilmslow Rd, Manchester M20 4BX, UK
[2] The Christie NHS Foundation Trust, Wilmslow Rd, Manchester M20 4BX, UK
[3] Manchester University NHS Foundation Trust, Oxford Rd, Manchester M13 9WL, UK

Abstract

Background: Radiotherapy with or without concurrent chemotherapy is a standard of care treatment for patients with head and neck squamous cell carcinoma (HNSCC). Upon completion, patients are referred for a post-treatment ^{18}F-FDG PET/CT (Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography) scan to help guide ongoing management by assessing for the presence or absence of residual or recurrent disease and differentiating this from post-treatment inflammation. To improve objective reporting of response, we developed the Christie score. The study aims to assess the validity of the Christie score as a response assessment tool in patients with HNSCC and to compare its performance against the widely used Hopkins score.

Methods and materials: All newly diagnosed head and neck cancers between July 2018 and July 2020 were retrospectively reviewed. In total, 291 patients (224 men and 67 women) were included in the study. Patients with squamous cell carcinoma of the nasopharynx, oropharynx or oral cavity, hypopharynx or larynx were included. All other cell lineages or anatomical locations were excluded. Hopkins and Christie scores were applied to post-treatment PET/CT, and sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio assessed for each score. Fisher's exact tests and receiver-operating characteristic (ROC) curves were used to determine the ability of the Hopkins and Christie scores to differentiate residual or recurrent disease from treatment response. p values < 0.05 were considered to indicate statistical significance.

Results: 39 patients (13%) were confirmed to have residual or recurrent disease. This was significantly more likely in patients with positive Hopkins ($p < 0.0001$) and Christie ($p < 0.0001$) scores. The Christie score has a higher sensitivity (92% vs. 85%) and negative predictive value (99% vs. 97%) compared to Hopkins, though the differences were not statistically significant. Comparison of the ROC curves for the Hopkins and Christie score revealed no significant difference between the two scores' ability to discriminate patients with residual or recurrent disease from cases where disease is absent ($p = 0.382$). 'Subjectivity rates' of the 291 patients are as follows. Six patients

(2.1%; 95% CI 0.76–4.5%) were assigned borderline scores on the Hopkins criteria, compared to only a single patient (0.3%; 95% CI 0–1.9%) on the Christie criteria. The 'subjectivity rate' difference is 0.017 (95% CI −0.06 to 3.5%; $p=0.06$) and the ratio is 6.0 (95% CI 0.73–276; $p=0.07$).

Conclusion: Our study identifies three clear results: (a) the Christie score is an excellent treatment follow-up assessment tool; (b) it is comparable with current gold standard methodology showing no statistically significant differences in performance when compared with the Hopkins score; and (c) there was a lower rate of observer variation when using the Christie score, which is trending towards significance.

Keywords: Head and neck cancer, FDG PET/CT, Response assessment, Oncology

Background

Head and neck cancer (HNC) is the sixth most common cancer globally with approximately 891,000 annual cases, and is the seventh most common for mortality with approximately 458,000 deaths (Bray et al. 2024). Globally, incidence rates have increased in recent decades and causes include modifiable risk factors such as tobacco smoking and alcohol consumption, as well as the human papilloma virus (HPV) in oropharyngeal cancer (Gormley et al. 2022). In the UK, HNC incidence rates are projected to rise by 3% between 2023–2025 and 2038–2040 (Cancer Research UK 2024).

Radiotherapy with or without concurrent chemotherapy is the standard of care treatment for patients with head and neck squamous cell carcinoma (HNSCC). Upon completion, patients are followed up clinically and radiologically. Clinical follow up can be challenging with patients experiencing non-specific symptoms and imaging helps guide ongoing management by assessing for residual/recurrent disease and differentiating this from post-treatment inflammation. In doing so, it helps to avoid unnecessary neck dissection where post-treatment imaging suggests complete metabolic response (King et al. 2011; Gupta et al. 2011; Mehanna et al. 2016). For example, the PET-NECK trial found that survival in patients with advanced nodal disease (stage N2 or N3) was similar among patients who underwent PET-CT-guided surveillance and those who underwent planned neck dissection, but surveillance resulted in considerably fewer operations and was more cost-effective (Mehanna et al. 2016). It revealed that PET-CT surveillance resulted in far fewer operations with approximately 80% of patients spared neck dissection. Moreover, patients in the surveillance group were not disadvantaged by undergoing delayed neck dissection.

At our institution, patients are referred for a post-treatment ^{18}F-FDG PET/CT (Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography) scan to assess for treatment response. Current best practice indicates this should be performed after a minimum period of 12 weeks to decrease false positive PET/CT results due to residual post-radiotherapy inflammation, concordant with current literature (King et al. 2011; Gupta et al. 2011; Seng et al. 2008; Marcus et al. 2014; Lonneux et al. 2000).

Several response assessment criteria have been devised for post-treatment HNSCC (Bonomo et al. 2020; Goel et al. 2017; Zhong et al. 2020; Banks et al. 2020; Aiken et al. 2018; Wong 2008). A response assessment score with a high negative predictive value (NPV) reassures both the patient and clinician that residual or recurrent disease is

Table 1 Hopkins score

Score	^{18}F-FDG uptake pattern	Response category
1	Uptake at primary site and nodes less than internal jugular vein (IJV)	Complete metabolic response
2	Focal uptake at primary site and nodes greater than IJV but less than liver	Likely complete metabolic response
3	Diffuse uptake at primary site or nodes greater than IJV or liver	Likely post-radiation inflammation
4	Focal uptake at primary site or nodes greater than liver	Likely residual tumour
5	Focal and intense uptake at primary site or nodes	Residual tumour

Table 2 Christie score

Score	^{18}F-FDG uptake pattern	Response category
1	Uptake at primary site and nodes $\leq 1 \times$ mediastinal blood pool (MBP)	Complete metabolic response
2	Uptake at primary site and nodes $> 1 \times$ but $\leq 2 \times$ MBP	Likely post-treatment inflammation
3	Uptake at primary site and nodes $> 2 \times$ MBP	Residual/recurrent disease

absent (Gupta et al. 2011). The five-point Hopkins score (Marcus et al. 2014), a widely used metric, has substantial inter-observer agreement and excellent negative predictive value. However, it requires measurement of both internal jugular vein (IJV) and hepatic activity, as well as expert training in interpreting discriminators for focal or diffuse disease (Table 1).

To improve objective reporting of response, we developed the Christie score (Table 2), a three-point scale which compares tumour bed activity with one reference point, the background mediastinal blood pool activity (MBP), a standard non-subjective reference. The Christie score is designed to be easy to use and interpret but with comparable accuracy to previously designed criteria. The study aim was to assess the validity of the Christie score as a response assessment tool in patients with HNSCC and to compare its performance against the Hopkins score.

Methods and materials

Ethics

This was registered as a clinical service evaluation project at our institution [REF: 3174].

Cohort

All newly diagnosed head and neck cancers between July 2018 and July 2020 were retrospectively reviewed. Patients with biopsy-confirmed squamous cell carcinoma of the nasopharynx, oropharynx or oral cavity, hypopharynx or larynx were included. All other cell lineages or anatomical locations were excluded. Available initial post-treatment PET/CT scans for the included patients were reviewed for analysis. Electronic patient records were reviewed to interrogate subsequent patient follow up where required.

Classification

Scans were interpreted by four consultant radiologists specialising in head and neck oncological radiology, and an FRCR-certified (Fellow of the Royal College of

Table 3 Patient demographics

Characteristic	N (%)
Sex	
Male	224 (77.0)
Female	67 (23.0)
Site	
Oropharynx	178 (61.2)
Hypopharynx	41 (14.1)
Larynx	30 (10.3)
Oral cavity	22 (7.6)
Nasopharynx	15 (5.2)
Unknown	5 (1.7)
HPV status	
Positive	144 (49.5)
Negative	43 (14.8)
Unknown	104 (35.7)
Age (years)	
Mean	61.7
Standard deviation	10.2
Median	61
Interquartile range	55–68

Table 4 Hopkins score applied to our patient cohort

Hopkins score	Recurrent or residual disease	No recurrent or residual disease
Test positive (4–5)	33 (TP)	41 (FP)
Test negative (1–3)	6 (FN)	211 (TN)

TP: true positive, FP: false positive, FN: false negative, TN: true negative, Test positive: Hopkins score 4–5; Test negative: Hopkins score 1–3

Table 5 Christie score applied to our patient cohort

Christie score	Recurrent or residual disease	No recurrent or residual disease
Test positive (3)	36 (TP)	47 (FP)
Test negative (1–2)	3 (FN)	205 (TN)

TP: true positive, FP: false positive, FN: false negative, TN: true negative. Test positive: Christie score 3; Test negative: Christie score 1–2

Radiologists) senior radiology registrar. Hopkins and Christie scores were obtained by measuring SUV_{max} (standardised uptake value) over regions of interest at the primary tumour or nodal site and comparing to reference SUV_{max} values at the IJV (internal jugular vein), the mediastinal blood pool (measured in the ascending aorta at the level of the pulmonary trunk) and the background hepatic activity.

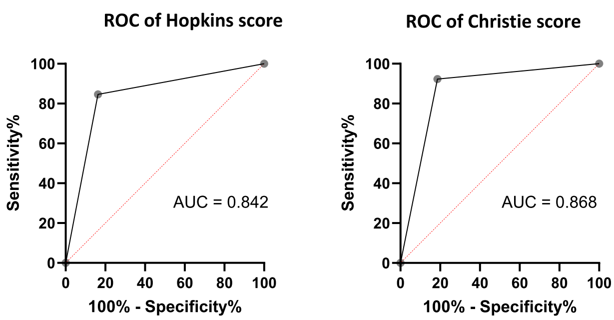
Christie score was calculated by measuring SUV_{max} at two points; the primary region of interest (tumour or nodal site) and the mediastinal blood pool reference. Unlike the Hopkins score, the Christie score does not require measurement of the IJV SUV_{max}, nor does it require subjective assessment of whether lesional tracer uptake is focal or diffuse.

Table 6 A comparative analysis of Hopkins and Christie scores

	Hopkins score		Christie score	
	Value	**95% CI**	**Value**	**95% CI**
Sensitivity	0.846	0.703–0.929	0.923	0.797 to 0.974
Specificity	0.837	0.787–0.878	0.814	0.761 to 0.857
PPV	0.446	0.338–0.559	0.434	0.332 to 0.541
NPV	0.972	0.941–0.987	0.986	0.959 to 0.996
Likelihood ratio	5.201		4.95	

Sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio for the Hopkins and Christie score at determining recurrent or residual disease. CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value

Table 7 ROC curve analysis of the two scores



The scoring system was binarized for analysis. Hopkins scores of 4 and 5, and Christie scores of 3 were considered suspicious for residual or recurrent disease. The remaining scores were considered to reflect an absence of residual or recurrent disease, i.e. test negative. Cases that were attributed a 'borderline score', e.g. Hopkins 3/4 or Christie 2/3, were classified based on the higher number.

Cases defined as positive for residual/recurrent disease were confirmed either histologically (through biopsy or surgical excision) or from a combination of positive radiology and clinical follow up within 6 months of post-treatment PET/CT.

The number of cases assigned a borderline score was used to quantify observer variation and determine a 'subjectivity rate'; defined as number of cases recorded with a borderline score/total number of cases.

Statistics

Statistical analyses were performed using Prism v10.2 (GraphPad) and Stata v13.0 (StataCorp). Descriptive statistics are presented as mean (± standard deviation) if parametrically distributed, or median and interquartile range (IQR) if nonparametrically distributed. Normality was determined using the D'Agostino-Pearson test. Sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio were calculated for the Hopkins and Christie scores; along with their respective 95% confidence interval (CI). Fisher's exact tests and receiver-operating characteristic (ROC) curves were used to determine the ability of the Hopkins and Christie score to differentiate residual or recurrent disease from treatment response. The area under the ROC curves (AUC) was calculated. ROC curves were compared using the Hanley and McNeil method (Hanley and McNeil, 1983). 'Subjectivity rates' were analysed using MedCalc Software Ltd version 23.0.2. The difference between, and the ratio of, the two rates are reported, along with their Poisson 95% confidence intervals.

P values < 0.05 were considered to indicate statistical significance.

Results

In total, 291 patients (224 men and 67 women) with biopsy-proven HNSCC were included in the study. The median age was 61 years (IQR 55–68). The median time between the end of treatment and the post-treatment PET/CT was 12.7 weeks (IQR 12.0–14.3). A tabulated list of patient demographics is provided in Table 7.

39 patients (13%) were confirmed to have residual or recurrent disease. This was significantly more likely in patients with positive Hopkins (p < 0.0001) and Christie (p < 0.0001) scores.

Two by two confusion matrices were derived for both Hopkins (Table 4) and Christie scores (Table 5). The sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for each criterion are shown in Table 6. Of note, the Christie scoring method has a higher sensitivity (92% vs 85%) and negative predictive value (99% vs. 97%), though the differences were not statistically significant.

The ability to discriminate patients with residual or recurrent disease was quantified on ROC analysis (Table 7). This revealed an AUC of 0.842 (95% CI 0.771–0.912) for the Hopkins score and 0.868 (95% CI 0.811–0.925) for the Christie score. Comparison of the ROC curves for the Hopkins and Christie score revealed no significant difference between the two scores' ability to discriminate patients with residual or recurrent disease from cases where disease is absent (p = 0.382).

'Subjectivity rates' of the 291 patients are as follows. Six patients (2.1%; 95% CI 0.76–4.5%) were assigned borderline Hopkins scores, compared to only a single patient (0.3%; 95% CI 0–1.9%) on the Christie score. The 'subjectivity rate' difference is 0.017 (95% CI − 0.06 to 3.5%; p = 0.06) and the ratio is 6.0 (95% CI 0.73–276; p = 0.07).

Discussion

Our study identifies three clear results: (a) the Christie score is an excellent treatment follow-up assessment tool; (b) it is comparable with the current gold standard methodology showing no statistically significant differences in performance; and (c) there was

(See figure on next page.)

Fig. 1 Case 1—MIP images from pre- and post-treatment PET/CT examinations are shown on the top row. Pre-treatment PET/CT (left image, row 2) shows a bulky FDG avid right cervical nodal mass. Post-treatment PET/CT (right image, row 2) demonstrates residual soft tissue in the neck; a Christie score of 2 was attributed to post-treatment inflammation; SUV max in the neck was measured at just under twice the MBP SUV max (4.2 in neck vs. 2.2 MBP). Patient underwent an MRI of the neck the following month which reported possible small volume residual disease within right sided cervical nodes (left image, row 3). The patient was placed on surveillance and further MRI 5 months later was reported as reassuring (right image, row 3). A CT neck performed 1 year after initial post-treatment PET/CT reported large volume recurrent disease in the right neck (bottom row), confirmed at neck dissection. This case likely represents early recurrence rather than residual disease, given the reassuring interval MRI

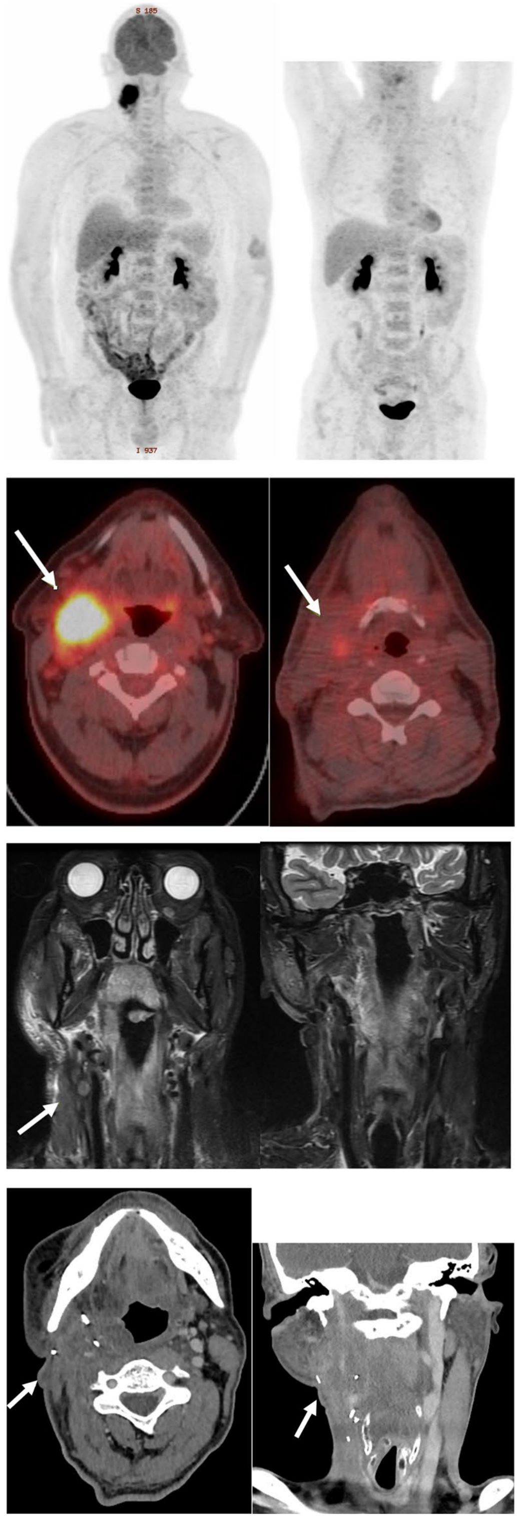


Fig. 1 (See legend on previous page.)

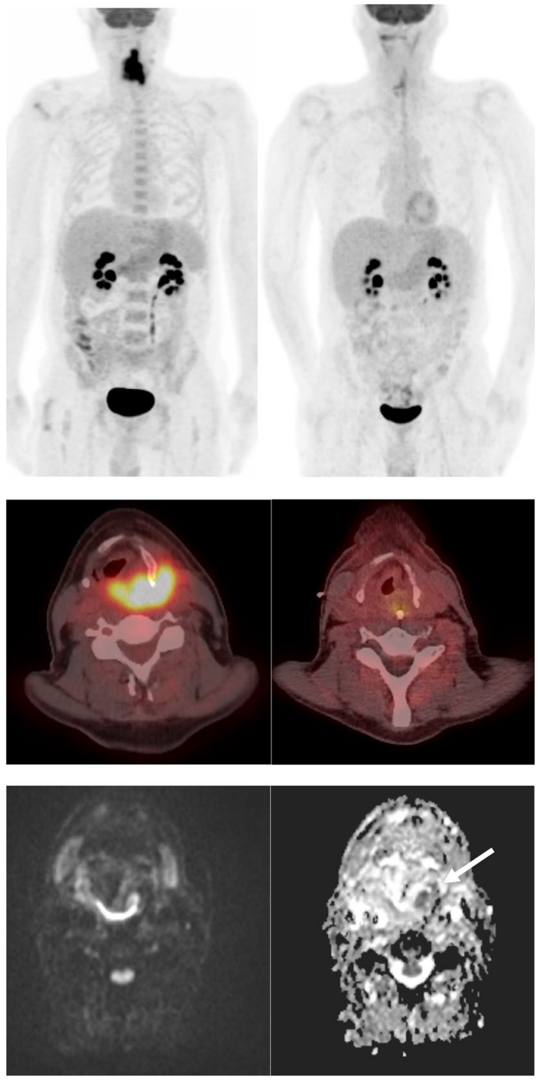


Fig. 2 Case 2—MIP images from pre- and post-treatment PET/CT examinations are shown on the top row. Pre-treatment PET/CT shows a bulky FDG avid hypopharyngeal tumour (left image, row 2). Post-treatment PET/CT shows response with assigned Hopkins score of 3 and Christie score of 2, both in concordance and suggestive of post-radiation inflammation (right image, row 2). Interval imaging surveillance was suggested, and a subsequent MRI neck reported left hypopharyngeal thickening consistent with post-treatment change. Flexible nasal endoscopy performed the following month showed residual candidiasis along the left pharyngeal wall. A further interval MRI neck performed three months later (bottom row) demonstrated diffusion abnormalities suspicious for recurrent disease which was subsequently proven histologically. As disease was confirmed within 6 months of post-treatment PET/CT this was assigned as a false negative for both Hopkins and Christie scores. Because the patient had both reassuring imaging and visual inspection initially, it may be that this was a case of early recurrence rather than residual disease; if so, this would mean that at the timepoint of the first post-treatment PET/CT there may have been no disease present

a lower rate of observer variation with the Christie scoring system, which is trending towards significance.

Using the Christie score in our patient cohort yielded a high NPV of 98.6%. Of all 291 patients in the study, there were only 3 false negative cases where residual/recurrent disease was present despite a negative Christie score. In comparison, there were

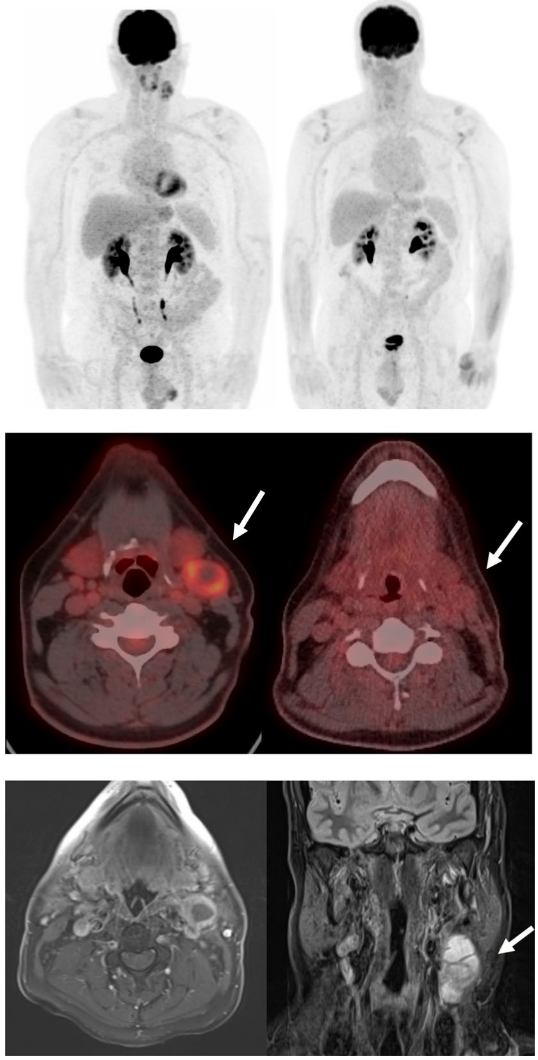


Fig. 3 Case 3—a patient with a primary tongue base tumour and involved necrotic cervical lymph nodes. Pre- and post-treatment MIP images are shown on the top row. Pre-treatment PET/CT (middle left) shows a centrally necrotic left cervical node. Post-treatment PET/CT (middle right) reported a complete response at the primary site with a persistent necrotic left level II cervical lymph node confirmed on MRI (bottom row). Hopkins and Christie scores were concordant, both scoring 2, suggestive of complete metabolic response/post-radiation inflammation. Following MDT (multidisciplinary team) discussion, the patient was referred for a limited excision of the necrotic left neck node which demonstrated residual microscopic nodal disease (ypT1) and extensive post-radiation inflammation

6 false negative cases when the Hopkins score was applied. Of the three false negative cases identified by the Christie score (demonstrated in detail in Figs. 1, 2, 3), two patients had close follow-up (imaging and nasal endoscopy) initially suggestive of post-treatment appearances, with disease only becoming clinically evident at 5 (Fig. 1) and 12 months (Fig. 2) post completion of chemoradiotherapy. These may therefore have been truly negative at the time of the PET/CT and may represent early recurrences rather than residual disease. For the third patient, post-treatment PET/CT demonstrated a persistent necrotic left level II cervical lymph node. Hopkins and Christie scores were concordant, both scoring 2, suggestive of complete metabolic response/post-radiation inflammation.

Following multi-disciplinary team (MDT) discussion, the patient was referred for a limited excision of the residual node which demonstrated residual microscopic nodal disease (ypT1) and extensive post-radiation inflammation. It is worth noting that necrotic nodes are a recognised pitfall in post-treatment response assessment PET/CT as they may demonstrate reduced activity on ^{18}F-FDG PET/CT, which can lead to false negatives on response assessment PET/CT (Saindane 2013). For this reason, necrotic nodes should be interpreted with caution. Ultrasound-guided fine needle aspiration of necrotic nodes can be useful for troubleshooting in these cases.

In three cases, there was discordance where the retrospectively assigned Christie score suggested residual/recurrent disease, but the Hopkins score indicated post-radiation inflammation. Residual disease was subsequently diagnosed between 2 and 7 months later. Had these patients been assigned a Christie score in practice, further assessment may have been triggered at the timepoint of the first post-treatment PET/CT scan, potentially leading to earlier diagnosis. Two example cases are demonstrated in Figs. 4, 5.

The trade-off of the Christie score's high NPV is a slight increase in false positives which reduces specificity. Using the Christie score instead of the Hopkins score results in similar false positive reports (47 cases, vs. 41 when applying the Hopkins score; not statistically significant). False positive cases may lead to patient distress or in extreme cases unwarranted surgery. However, our experience locally is that all PET/CT positive cases are discussed in a specialist MDT meeting. When there is clinical uncertainty around management, i.e. post-radiation inflammation versus residual/recurrent disease, patients often undergo close clinical follow up followed by a repeat PET/CT.

The high NPV of the Christie score means that it is a valuable tool to aid in the exclusion of residual/recurrent disease in the setting of post-treatment PET/CT in HNSCC. It could be argued that the slightly increased number of false positive cases is a reasonable trade-off for the increase in NPV and associated reduction in missed cases of residual/recurrent disease, particularly when over-calling post-radiation inflammation as disease on a response assessment PET/CT can result in closer observation and interval assessment with PET/CT.

(See figure on next page.)

Fig. 4 Case 4—a patient with T4b N2b M0 oropharyngeal SCC. Top row shows pre- and post-treatment MIP images. Fused PET/CT on the pretreatment scan (row 2, left image) shows extensive primary tumour. Post-treatment response assessment PET/CT (row 2, right image) reported a favourable response to treatment, with an assigned Hopkins score of 3 suggesting post-treatment inflammation. However, a Christie score of 3 assigned to this case would have flagged up as likely residual/recurrent disease. Concurrent MRI neck also reported likely post-treatment change and advised surveillance imaging (images not included). Discussion in the head and neck MDT noted some residual changes in the left mandible but no significant uptake on PET/CT and recommended ongoing surveillance. A follow up PET/CT performed three months after initial post-treatment PET/CT noted improving post-treatment appearances but with prominent activity within the left mandible. Further MRI and PET/CT examinations reported progressive bulkiness of the left pterygoid muscle with soft tissue extension into the left mandibular ramus which demonstrated ongoing bone destruction (3rd & 4th rows). A possibility of radiation necrosis was raised. The patient was reviewed in the ENT (ear, nose and throat) clinic and an orthopantomogram confirmed a fracture at the angle of the mandible (bottom row), considered secondary to osteoradionecrosis. Biopsies from the left retromolar trigone and US guided biopsy of the floor of mouth subsequently demonstrated recurrent/residual disease

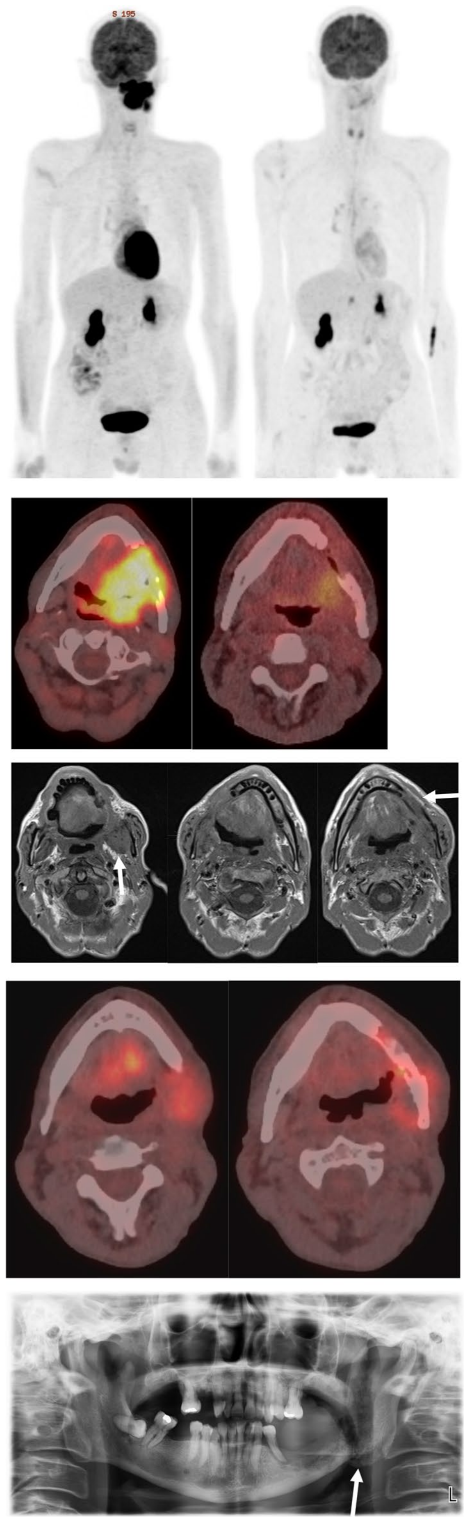


Fig. 4 (See legend on previous page.)

One of the favourable features of the Christie score is the ease of implementation. The IJV is not always a reproducible reference point for blood pool activity; it is a small target compared to the ascending aorta where the mediastinal blood pool is measured

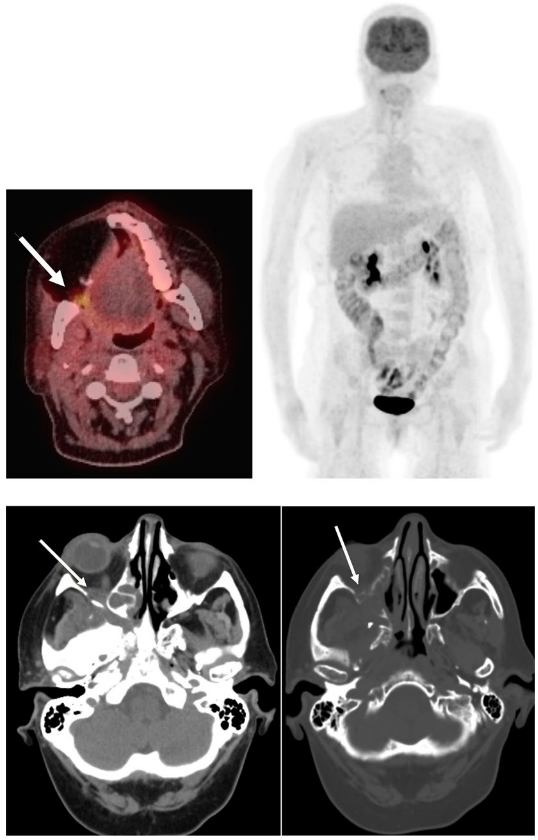


Fig. 5 Case 5—a patient with T4 N3 M0 oral cavity squamous cell carcinoma underwent post-treatment PET/CT (top row). Residual activity reported in the right retromolar trigone was assigned a Hopkins score of 3 suggestive of post-treatment inflammation. A Christie score of 3 applied retrospectively to this case would have flagged up as residual/recurrent disease. An external CT head performed after three months (bottom row) demonstrated residual/recurrent disease in the skull base with evidence of perineural spread

and is particularly difficult to measure in the presence of brown fat uptake, which can also mimic disease (van Marken Lichtenbelt et al, 2009). The IJV can also be challenging to identify in the post-treatment neck with background inflammation and distorted anatomy, for example, following neck dissection. By using the mediastinal blood pool as a reference point, the Christie score should improve uniformity and reproducibility of response assessment PET/CT reporting in the setting of HNSCC.

In a further bid to improve uniformity and reproducibility, the Christie score is reduced from the five-point system utilised by the Hopkins score to a simpler three-point system. The Hopkins score introduces a focal versus diffuse discriminator to try to help the reporter choose between more diffuse post-treatment change or focal high-grade uptake more commonly seen with disease. The Christie score removes this subjective discriminator, which may also help to reduce inter-observer variability. Further studies can help validate this. Whilst removing these additional quantifiers and stripping back to a simple three-point scoring system, application of the Christie score to our patient cohort has produced similar accuracy to the Hopkins score and an improved NPV of 99%. The reduced number of borderline scores awarded for the Christie score, as compared to Hopkins, may reflect its relative ease of use.

Our analysis touched on subjectivity rates between observers but did not look in depth at inter-observer variability. Whilst we feel the Christie score is easy to implement, further assessment in a planned prospective study can validate this by analysing inter-observer variability when using the Christie score. A larger, prospective multi-centre trial will help to further validate the Christie score as a clinically useful and reproducible tool in the assessment of patients with HNSCC following chemoradiotherapy.

Conclusions

In conclusion, the Christie score is a simple and reproducible response assessment tool in the setting of post-treatment PET/CT for patients with HNSCC. It demonstrates comparable results when compared with the Hopkins score and has a high NPV which is useful to aid in the detection of residual/recurrent disease and minimise unnecessary intervention.

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Author contributions
NB– data collection, analysis, write-up, manuscript review & editing. SB—data collection, overseeing project, manuscript review. CB, SM, AC—data collection, manuscript review. AD—statistical analysis, manuscript review. RN—statistical analysis. JP—review of manuscript. GB—data collection.

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Competing interests
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