Verification of the Efficacy of New Diagnostic Criteria for Retropharyngeal Nodes in a Cohort of Nasopharyngeal Carcinoma Patients

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Research

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Abstract

Background: A multistage approach to diagnose lateral retropharyngeal nodes (LRPNs) of nasopharyngeal carcinoma (NPC) had been proposed and warranted for validation.

Methods: From 2012 to 2017, we collected NPC cases with LRPNs before radiotherapy-based treatments. The responsive nodes or those that progressed during follow-up were positive. The proposed criteria for the multistage approach delimited LRPNs with a minimal axial diameter (MIAD) ≥ 6.1 mm were positive and if the mean standard uptake value ≥ 2.6, or if the maximal coronal diameter ≥ 25 mm and maximal axial diameter ≥ 8 mm with nodes MIAD < 6.1 mm were also positive. The outcomes were compared with the MIAD cutoff value ≥ 6 mm (traditional method). Chi-squared test was used to compare two areas under the curve (AUC) of receiver operating characteristic curves.

Results: A total of 67 eligible NPC cases and 155 LRPNs (72 positive and 83 negative) were analyzed. The accuracy, specificity, and sensitivity of the traditional method were 0.91, 0.93, and 0.89, respectively. The values for the multistage approach all reached 0.94. The AUC was significantly greater for the multistage approach compared with that for the traditional method ($p = 0.023$).

Conclusion: The results of LRPN data in this cohort of patients support the advantage of the multistage approach.

Background

The accurate diagnosis of lateral retropharyngeal nodes (LRPNs) with images for nasopharyngeal carcinoma (NPC) is important. Magnetic resonance imaging (MRI) is a standard choice for detecting LRPNs in NPC [1]. Based on control subject analysis, Lam and King used minimal axial diameter (MIAD) (4 and 5 mm, respectively) as the upper limit of normal LRPNs [2, 3]. A diameter of 5 mm or higher as a criterion of malignancy was widely cited in Science Citation Index papers dealing this issue [4–12]. Following Zhang's article, given the response to radiotherapy (RT) and follow-up data analysis, a new criterion of ≥ 6 mm diameter has been considered more accurate for malignant nodes [13]. The method proposed by Zhang was reviewed as a "robust standard methodology" [14]. The said method was also tested by the power of prognosis prediction [15]. The newly proposed size criterion for malignant LRPNs minimally up-shifted the definition of LRPN involvement from "≥ 5 mm" to "> 5 mm," with the consensus of an international guideline for NPC [16] and several publications [17–20]. However, based on the prognostic value of LRPN metastasis laterality, a recent study favored ≥ 5 mm as more suitable than ≥ 6 mm as the cutoff value of MIAD [21]. The inconsistency of results in the above published data characterizing LRPNs implies that when only a single factor is used to determine the malignancy of LRPNs, the power of detection could be limited. FDG PET/CT, with its functional imaging sensitivity in detecting cancerous nodal lesions, may be complementary to MRI, which was highly encouraged in the 2017 American Joint Committee on Cancer (AJCC) staging system [22]. Previously, we proposed a new set of diagnostic criteria of parameters combined mean standard uptake value (SUV_{mean}) from PET/CT

and MR (MIAD, maximal axial diameter (MAAD), and maximal coronal diameter (MACD)) with a significant higher reported accuracy although an external cohort validation may be warranted [23]. Using a multistage approach to assess a node in daily practice is cumbersome. Thus, the superiority of the new criteria in validating other groups of patients must be verified to convince clinicians to accept them. This study aimed to validate the efficacy of the multistage approach to diagnose LRPNs with a new cohort of NPC cases in our hospital.

Methods

Patients and treatment

From Oct 2012 to Dec 2017, we retrospectively collected data of NPC cases with medical charts and image data to analyze the LRPN characteristics. Newly diagnosed NPC cases were enrolled. Exclusion criteria included cases without MRI or PET and examining dates within 3 weeks and before starting any cancer treatment, cases with incomplete definitive RT dose (under 5940 cGy), those who did not undergo MRI within 3 months after the end of RT date, those whose initial MRI failed to reveal any LRPN, and those lacking tissue proof of NPC. Patients with additional head and neck cancers or acute inflammation were also excluded from this study. All patients received RT-based cancer treatment (including induction chemotherapy + concurrent chemoradiation (CCRT), CCRT ± adjuvant chemotherapy, or RT alone). RT was given with standard fractionations with dose ranging from 5940 cGy to 7200 cGy, with mean ± standard deviation (SD) = 7073 ± 166 cGy. All the patients received RT with intensity-modulated RT or volumetric arc therapy with an accelerator or TomoTherapy.

Imaging protocol and assessment

All patients underwent initial MRI and PET/CT. MRI and FDG PET/CT scans were conducted less than 3 weeks apart (mean ± SD = 2.5 ± 6.0; range: 0–17 days) before cancer treatment. The details of imaging protocols for MRI (Siemens Medical Systems, Erlangen, Germany) and PET/CT (GE Healthcare, Chicago, IL, USA) and the methods of measurement of nodal parameters were identical to those described in our previous reports [23, 24]. Three experienced NPC physicians (Yu-Wen Wang, Yu-Cheng Hung, and Yu-Kang Chang) evaluated the data in this study. Yu-Wen Wang is an experienced radiation oncologist. Yu-Cheng Hung is a board-certified nuclear-medicine physician. Yu-Kang Chang is a senior board-certified diagnostic radiologist. These practitioners were blind to patient details. Yu-Wen Wang and Yu-Cheng Hung evaluated both MRI images and the corresponding FDG PET/CT data and the SUV_{mean} of the FDG PET/CT data for the region of interest using the MRI image as an anatomical reference. Any disagreements were resolved by consensus among the three physicians.

Follow-up and Assessment of Lymph Nodes

The images of LRPNs of patients were reviewed. We observed the response of these nodes before and after RT-based local treatment by serial MRI. Repeated MRI was performed within 1–2 months (mean ± SD = 43.9 ± 15.7; 6–85 days) after RT. Positive nodes could be identified for patients with a follow-up of

less than 6 months. Patient observation for absence of nodal recurrence for period longer than 6 months was needed if negative nodes could be diagnosed. Overall, the follow-up period after RT ranged from 0.2 month to 84.4 months (mean ± SD = 30.1 ± 20.9). We measured the changes in MAAD and MACD before and after the treatment to determine the nature of nodes [23, 25]. The responsive nodes and those that progressed during follow-up were positive; otherwise, the nodes were considered negative (Fig. 1). The images of widely accepted characteristics of involved node, as recommended by international consensus of delineation of target volume for NPC extracapsular extension (ECE), central necrosis (CN), and three or more contiguous confluent (grouping) LRPNs in MRI and overt FDG avid node in PET/CT, were also recorded in addition to the nodal diameter measurement for result comparison [16].

Currently, we think that the optimal conventional method with a single parameter criterion (MIAD ≥ 6.0 mm) yielded positive results, although we also tested the outcome results by using MIAD ≥ 5.0 mm for comparison [13–15, 23]. The proposed new criteria with the multistage approach included MIAD and SUV_{mean} as factor from PET scan and other parameters from MRI (MAAD and MACD). The LRPNs with a MIAD ≥ 6.1 mm were considered positive. If the SUV_{mean} ≥ 2.6 or if the MACD ≥ 25 mm and MAAD ≥ 8 mm, then the nodes with MIAD < 6.1 mm were positive [23]. Otherwise, they were negative (Fig. 2).

Statistical Analysis

The scatter plots for each parameter for LRPNs for positive and negative nodes were illustrated with Excel 2010 version 14.0.7212.5000 (Microsoft, Redmond, WA). The new approach and MIAD ≥ 6.0 mm were tested to derive the respective accuracy for LRPNs, which were indicated by the areas under curve (AUC) of each receiver operating characteristic curve. For comparison of the small difference between the two methods, the significance of difference between the two AUCs from both approaches was calculated by Chi-squared test with the null hypothesis considering the two AUC as equal. The statistical analyses were carried out using SAS 9.4 (Cary, NC, USA)

Results

A total of 137 patients were initially enrolled for the investigation. Table 1 lists the 67 eligible NPC cases and their clinical characteristics. Among the 155 LRPNs identified from these patients, 72 were positive, and 83 were negative (Fig. 1, with an additional table showing this in more detail [see Additional file 1]). All positive and negative nodes for MIAD, MAAD, MACD, and SUV_{mean} were separately drawn with scatter plots (Fig. 3, with additional tables showing these in more detail [see Additional file 2 and 3 respectively]). The accuracy, specificity, and sensitivity from two traditional MIAD cutoffs at ≥ 5 mm reached 0.85, 0.74, and 0.97, respectively. The values at ≥ 6 mm were 0.91 (accuracy), 0.93 (specificity), and 0.89 (sensitivity). The accuracy, specificity, and sensitivity for the multistage approach were all 0.94 (Table 2). Compared with that of the traditional method, the AUC (Fig. 4) was significantly greater for the multistage method with a cutoff at ≥ 6 mm with p = 0.023. In our series, 28 LRPNs with a picture of node groupings, 39 ECE, 44 CN, and 40 overt FDG uptake LRPNs were obtained and identified as positive nodes. There is an additional table showing this in more detail [see Additional file 4].

Table 1
Clinical characteristics of 67 eligible nasopharyngeal carcinoma patients.

Characteristic	Number of patients (percentage)
Age (years)	
Age < 40	15 (22)
Age ≥ 40	52 (78)
Sex	
Male	46 (69)
Female	21 (31)
World Health Organization pathologic feature	
Keratinizing squamous cell carcinoma	0 (0)
Non-keratinizing carcinoma (not otherwise specified)	9 (13)
Non-keratinizing differentiated carcinoma	23 (34)
Non-keratinizing undifferentiated carcinoma	34 (51)
Not applicable	1 (1)
American Joint Committee on Cancer 2010 stage	
I	3 (4)
II	11 (16)
III	23 (34)
IV	30 (45)

Table 2
Accuracy results of multistage and conventional criteria for 155 lateral retropharyngeal nodes in our patients.

Criteria for 155 nodes	Accuracy	Specificity	Sensitivity	Positive predictive value	Negative predictive value
MIAD ≥ 5.0 mm	0.845	0.735	0.972	0.761	0.968
MIAD ≥ 6.0 mm	0.910	0.928	0.889	0.914	0.906
Multi-stage method	0.942	0.940	0.944	0.932	0.951
MIAD, minimal axial diameter					

Discussion

Zhang's noticeable proposal for shifting MIAD ≥ 6 mm from ≥ 5 mm has still not gained worldwide acceptance for clinical use due to the related survival data and its inconsistency [13–15, 21]. Given that specificity and sensitivity can never be enhanced simultaneously by tuning a single parameter, problems will remain unsettled if we do not consider adding other parameters for assessment. The results listed in Table 2 showed better diagnostic outcomes compared with those from using either MIAD ≥ 6 mm or ≥ 5 mm. The outperformance of multistage approach reinforced the superiority of applying the same method Wang first proposed [23]. Compared with the results of the original cohort from our previous study (Table 3), the current findings were better in all outcome categories. A possible explanation was that the tested nodes might be easier to be judged in this cohort. However, the common advantage of both cohorts for multistage method over a single parameter was the enhancement of specificity and sensitivity, different from shifting a single cutoff value from 5 mm to 6 mm that results in the sacrifice of sensitivity.

Table 3
Results of multistage and two conventional criteria for 410 nodes in our previous report [23].

Criteria for 410 nodes	Accuracy	Specificity	Sensitivity	Positive predictive value	Negative predictive value
MIAD ≥ 5.0 mm	0.846	0.779	0.910	0.814	0.891
MIAD ≥ 6.0 mm	0.890	0.930	0.853	0.928	0.856
Multi-stage method	0.905	0.950	0.863	0.948	0.867
MIAD, minimal axial diameter					

The role FDG-PET/CT alone in determining the involvement of LRPNs is seldom appreciated [24, 26]. However, as a component of multistage method, the overall accuracy of diagnosis can still be enhanced remarkably.

The major limitations of this study included the lack of radiologic–histopathologic correlation data. The feasibility of tissue proofing before ongoing chemotherapy or RT for LRPNs in newly diagnosed NPC is still lacking, although several biopsy methods had been reported; still, several procedures could be safe [27–31]. However, these procedures are only applied to the recurrent LRPNs and not for new cases before RT. The typical images of our nodes all agreed with the positive nodes by RT response follow-up data. Using the criteria for assessing LRPNs with RT response remains the robust standard methodology [14]. Second, the cases in our series were limited. Thus, different patient cohorts must be recruited to determine whether consistent results could be met. We did not have PET/MR, which could aid in the evaluation of the SUV_{mean} data in small nodes such as LRPNs [32–34]. We also did not consider other parameters, such as diffusion-weighted imaging in MRI and the effect of Epstein–Barr virus DNA serum titer [35, 36]. These parameters could be applied in future studies. Finally, the obtained accuracy

improvement from adopting the multistage method was relatively small but statistically significant. Given the lack of feasibility of resorting the final judgment of a LRPN to tissue proofing as backup in clinical treatment decision making for newly diagnosed NPC patients, clinicians are encouraged to apply this new method despite its long period of operation.

Conclusion

The results of LRPN data in this cohort of patients support the advantage of the multistage approach.

Abbreviations

AJCC: American Joint Committee on Cancer; AUC: Areas under the curve; CCRT: Concurrent chemoradiation; CN: Central necrosis; ECE: Extracapsular extension; FDG: (18)F-fluorodeoxyglucose; Grouping: Three or more contiguous confluent; LRPNs: Lateral retropharyngeal nodes; MIAD: Minimal axial diameter; MAAD: Maximal axial diameter; MACD: Maximal coronal diameter; MRI: Magnetic resonance imaging; NPC: Nasopharyngeal carcinoma; PET/CT: Positron emission tomography/computed tomography; RT: Radiotherapy; SUV_{mean}: Mean standard uptake value.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

DGT, WJY, CHC and YWW conceived the study concept and initiated the study design. DGT drafted this paper. HYC helped in analysis and interpretation of data. YSH, YKC and YWW made contributions for acquisition and analysis of data. YWW was the grant holder. YWW and HYC were involved in study implementation and critically reviewed the manuscript. All authors reviewed the manuscript and gave final approval of the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Chi Mei Medical Center (Approval numbers: 10710-L06). Although consent was not specifically obtained for this retrospective review, all information was anonymized and de-identified prior to its analysis.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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Figures

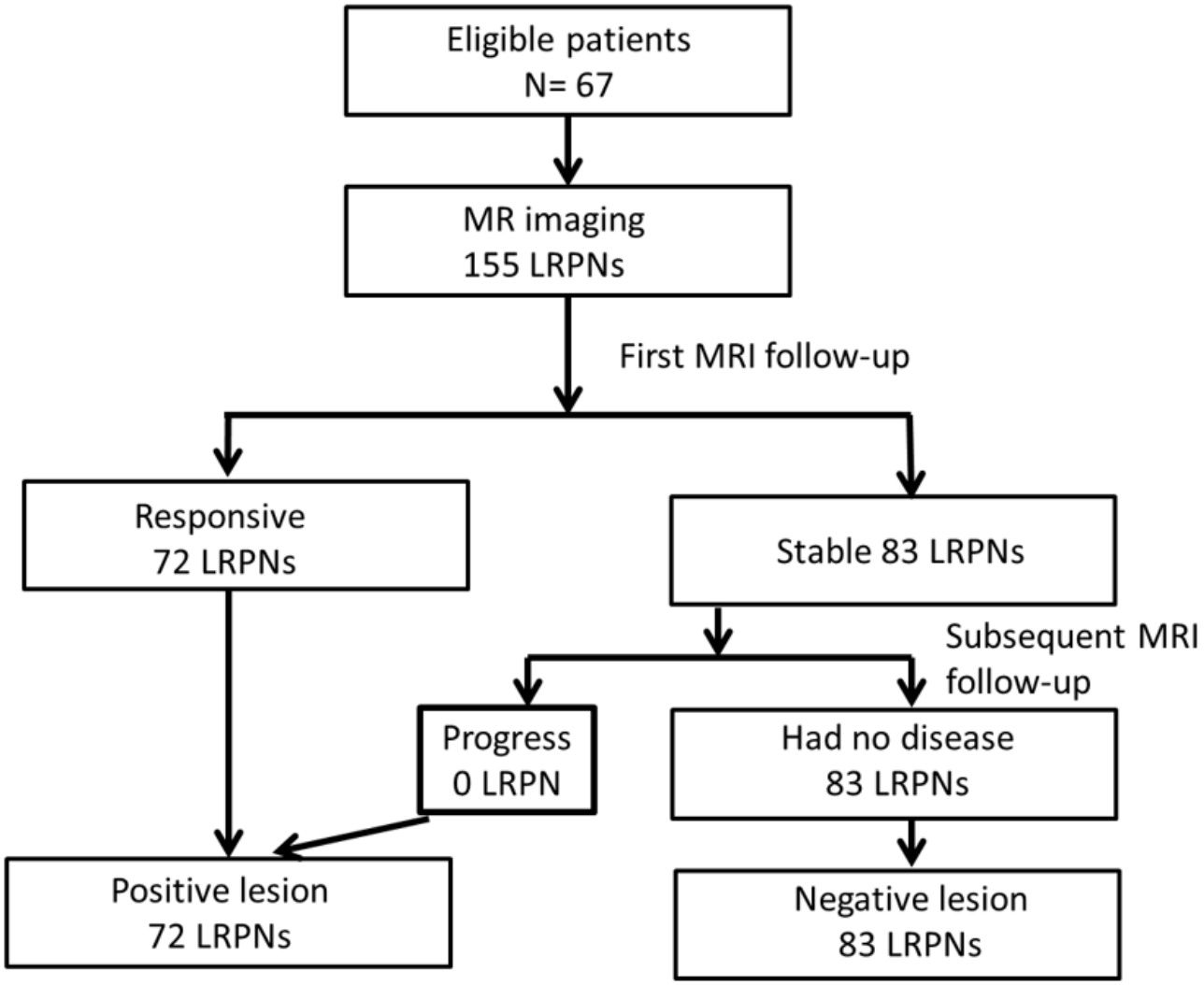

Figure 1

Flowchart outlining the follow-up. Flowchart outlining the follow-up MRI results of 155 lateral retropharyngeal nodes in 67 patients.

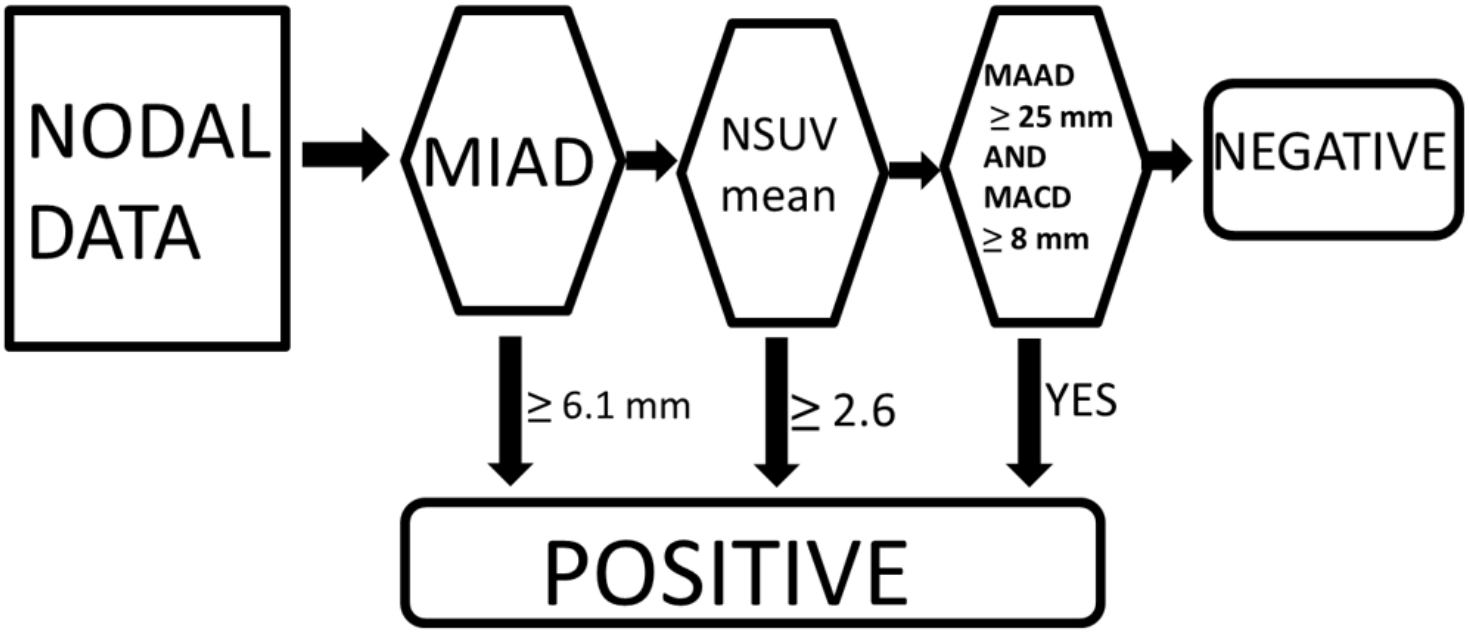

Figure 2

Multistage approach. Multistage approach with new criteria for lateral retropharyngeal nodes in retropharyngeal carcinoma.

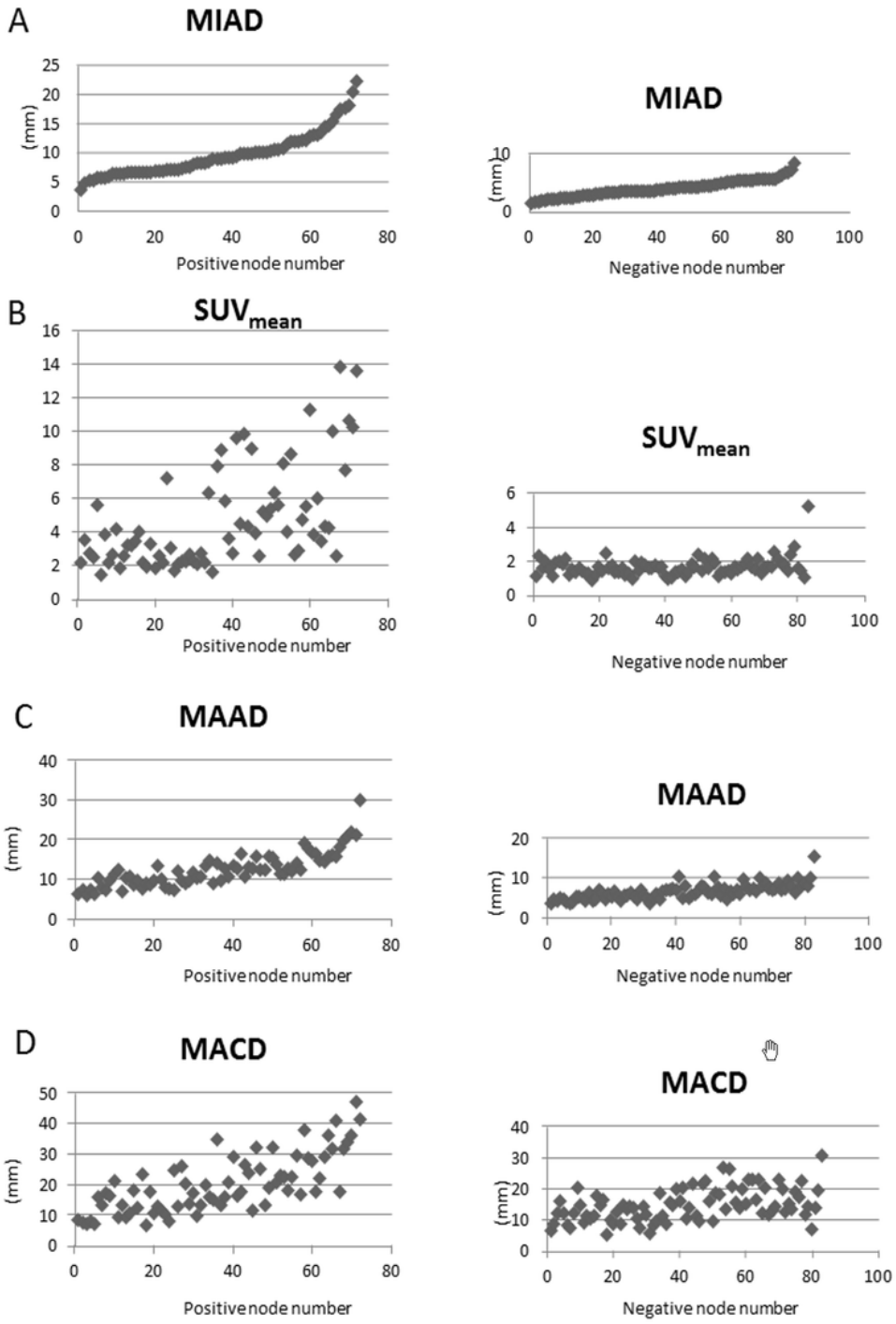

Figure 3

Scatter plots. Scatter plots of parameters versus 72 positive nodes on the left side and 83 negative nodes on the right side. A: We plotted the minimal axial diameter (MIAD) with the node numbers in abscissa ranked by the MIAD size. The values of other parameters (B: SUVmean; C: maximal axial diameter (MAAD); D: maximal coronal diameter (MACD)) are correspondingly plotted.

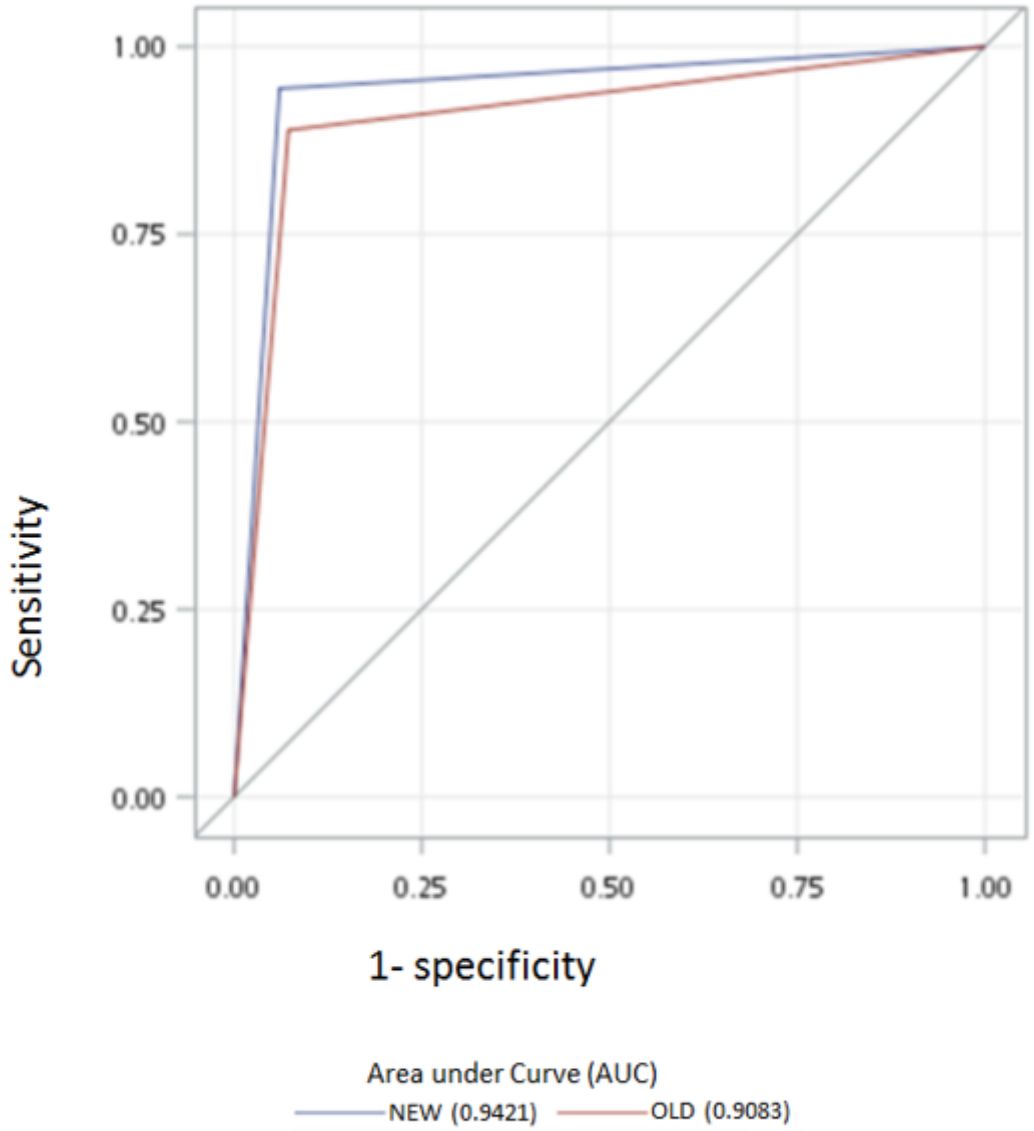

Figure 4

Receiver operating characteristic curves. Scatter plots for multistage approach (blue line) and old criterion using MIAD cutoff at ≥6 mm (red line).

Supplementary Files

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