COLORECTAL CANCER

High magnification chromoscopic colonoscopy or high frequency 20 MHz mini probe endoscopic ultrasound staging for early colorectal neoplasia: a comparative prospective analysis

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Background: Successful endoscopic management of early colorectal cancer using endoscopic mucosal resection requires the mandatory prediction of invasive depth and lymph node metastasis. Previous data using the Nagata crypt types Vn(B)/(C) as clinical indicators of T2/N+ disease have shown low specificity (50%) with a tendency to over stage lesions. New mini probe ultrasound "through the scope" imaging permits staging of lesions proximal to the rectum using direct endoscopic visualisation.
Aim: To compare the staging accuracy of the Nagata crypt type V with mini probe high frequency 20 MHz endoscopic ultrasound.
Methods: Sixty two patients with a Paris type II flat cancer were imaged using magnification colonoscopy followed by 20/12.5 MHz ultrasound in a "back to back" design. Crystal violet staining (0.05%) at $100\times$ magnification permitted Nagata crypt criteria to be defined. Submucosal deep invasion (sm3+) was defined at ultrasound by the presence or absence of a disrupted third sonographic layer. Predicted T0/1: N0 lesions were resected using endoscopic mucosal resection with the remaining referred for surgery. Ultrasound and magnification staging were then compared with the resected histopathological specimens.
Results: One patient was excluded from the study due to poor bowel preparation. Fifty two lesions from 52 patients therefore met inclusion criteria (12 sm1/13 sm2/27 sm3+). Ultrasound (20 MHz) was significantly more accurate for invasive depth staging compared with Nagata stage ($p<0.0001$) (overall accuracy 93% and 59%, respectively). The sensitivity for lymph node metastasis detection using ultrasound and magnification was 80% and 31%, respectively ($p<0.001$). The negative predictive value of ultrasound for invasive depth was better than that observed using magnification (88%/47%, respectively). The prevalence of nodal disease overall was 19% (10/52), with 80% (8/10) node positive lesions occurring in the sm3+ lesion group.
Conclusions: High frequency 20 MHz ultrasound is superior to magnification alone when differentiating T1/2 disease with a high positive predictive value for sm3 differentiation. Sm3+ invasion was associated with nodal metastasis.

Flat and depressed neoplastic lesions of the colorectum (Paris type (PT) II)[1] are now known to exist in Western populations.[2–7] Two UK based studies have shown prevalence rates of 22–38% in moderate to high risk colorectal cancer cohorts,[4 8] with the Sheffield group reporting high grade dysplastic characteristics in 25% of flat lesions proximal to the hepatic flexure, data substantiated by Lanspa and colleagues,[9] Smith and colleagues,[10] and Saito and colleagues.[5] Endoscopic mucosal resection (EMR) for "curative" intent is indicated for focal submucosal invasive neoplasia (submucosal-sm1) as lymph node metastases (LNM) are rare.[11 12] For PT II lesions vertically infiltrating sm layers 2 or 3, LNM rates exceed 10–15%.[12] Thus for EMR specimens the "cut off" value adopted by the Paris Workshop Group for quantitative micrometric measure is now assumed to be 1000 µm.[1] Successful endoscopic management of early colorectal cancer (CRC) using EMR therefore requires the mandatory prediction of invasive depth estimation and LNM identification.

Previous studies have addressed the efficacy of high magnification chromoscopic colonoscopy (HMCC) for the in vivo prediction of histopathological characteristics in PT type II lesions.[2 13–15] However, while offering adequate sensitivities for differentiation of hyperplasia from neoplasia, sensitivities

when predicting grade of dysplasia and invasive depth have been variable. In Hurlstone *et al*'s prospective analysis of sm invasion prediction[16] using the Nagata subclassification[17] of the Kudo type V crypt pattern,[13] the kappa coefficient of agreement between crypt type V(a–c) and histologically confirmed sm invasion was 0.51 (95% confidence interval). However, overall specificity was low at 50% with a tendency to over stage lesions.[16] In the clinical context this reflects a high false positive rate for anticipation of sm2+ disease, hence depriving some patients of the opportunity of curative endoscopic resection.

In comparison with HMCC staging, endoscopic ultrasound (EUS) using the 7.5 MHz radial probe has encountered similar problems with T stage accuracy, showing significant variability between groups (60–79%).[18 19] High frequency ultrasound (HFUS) staging using the 20 MHz through the scope (TTS) mini probe has however shown superior T staging characteristics for PT type II lesions with Saito *et al*

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Abbreviations: EMR, endoscopic mucosal resection; CRC, colorectal cancer; LNM, lymph node metastasis; HFUS, high frequency ultrasound; HMCC, high magnification chromoscopic colonoscopy; TTS, through the scope; IC, indigo carmine; CV, crystal violet; PT, Paris type; sm, submucosal; PPV, positive predictive value; NPV, negative predictive value

reporting a high overall accuracy of 88%.[20] Furthermore, Matsumoto et al demonstrated an overall accuracy of 91.8% and 63.3% for HFUS and HMCC, respectively.[21]

Our aim was therefore to prospectively assess the clinical utility and staging accuracy of HFUS imaging for PT type II lesions compared with HMCC Nagata criteria using standardised morphological, histopathological, and HFUS imaging criteria.

METHODS
Total colonoscopy using the Olympus CF240Z (Keymed, Southend-on-sea, UK) was performed prospectively on 52 patients with a known diagnosis of PT type II CRC from January 2003 to March 2005 by a single experienced endoscopist. Full ethics approval for the study was granted from the South Sheffield Research Ethics Committee (ref: SS/01/165). Written informed consent was obtained prior to the procedure. Bowel preparation comprised 2–4 litres of hypertonic polyethylene glycol solution (Kleanprep; Helix Bio-Pharma Corp, Aurora, Ontario, Canada) taken 24 hours prior to the procedure. Inclusion criteria were a previous diagnosis of a PT type II lesion identified at conventional colonoscopy with histological confirmation of carcinoma using standard biopsy sampling. Patients were excluded from the study if there was evidence of distant nodal disease (>10 mm diameter) at transabdominal computerised tomographic imaging or inability to provide written informed consent. All patients received a single 20 mg intravenous bolus of buscopan (hyoscine-N-butyl-bromide; Boehringer, Ingel-heim, Germany) once caecal intubation was achieved or on intubation of the neoterminal ileum in patients with a previous right hemicolectomy. Patients requesting conscious sedation received intravenous midazolam (1–10 mg) prior to intubation.

Study design
Each patient underwent a biphasic "back to back" examination with lesions initially staged using HMCC (phase 1) followed by duel frequency 12.5/20 MHz TTS HFUS imaging (phase 2). Targeted chromoscopy using 5–10 ml of 0.5% indigo carmine (IC) was used to delineate detailed morphology.[12] Lesions were classified morphologically according to the Paris Workshop guidelines.[1] Flat lesions were defined as mucosal change with a flat or slightly rounded surface with a height of less than half the diameter with no distinct stalk or pedicle (PT type II).[1] Lesion diameter was estimated using a standard fully open biopsy forcep (4 mm) with the height estimated by placing a closed biopsy forcep tip adjacent to the lesion margin (2.1 mm) (Bard Inc, USA).

Following morphological classification using IC chromoscopy, all identified lesions underwent high magnification imaging (×100) using 0.05% crystal violet (CV) solution. CV was applied following normal saline lavage and removal of residual mucous residue by localised application of 5 ml N-acetycystine (2 mg/ml) using the Olympus PW5V-1 non-traumatic steel tipped catheter. Following a "fixing phase" of 1–2 minutes, any excess CV was aspirated using gentle suction prior to high magnification imaging requisition. The surface pit pattern was subsequently classified according to the Nagata subclassification[17] of the Kudo type V crypt pattern.[13] Nagata grades A, B, and C were defined as crypt disorder fully defined, crypt disorder partially defined, and disorder not defined or absent, respectively.[17] The Nagata type C crypt was used as endoscopic criteria predictive of sm3, node positive disease.[16 17]

Following HMCC, all lesions underwent phase 2 HFUS imaging using the Olympus UM 2R 6 French 20 MHz and UM 3R 12.5 MHz TTS mini probe (Keymed). Acoustic coupling was achieved using the direct water immersion

technique or by the distal balloon attachment method of Tseng and colleagues.[22] Radial images were then acquired with invasion depth and nodal status classified according to the criteria of Cho and colleagues[23]:

- uT0: lesions confined to the first hypoechoic layer;
- uT1: lesion penetration to the third hypoechoic layer;
- uT2/3: lesion penetration of the muscularis propria (outer hypoechoic layer) or serosa (most peripheral echogenic band);
- uT4: lesion extension through the serosa with or without infiltration of adjacent structures; and
- u node positive (N+): presence of pericolic well demarcated hypoechoic round or oval structures >10 mm in diameter.

Histopathology and resection practice
All identified lesions were cold biopsied, removed by EMR,[2] or referred directly for surgical resection. Predicted T0/1/N0 lesions at HMCC or HFUS were resected using EMR (Roth net retrieval to minimise trauma and specimen fragmentation) with the remaining referred for surgical resection. An adjacent submucosal tattoo of Indian ink was applied to the latter group to enable operative localisation.

A single designated pathologist examined all specimens. Tissue was immediately fixed in 10% buffered formalin solution and subsequently stained with haematoxylin and eosin. Dysplasia was defined according to the modified Vienna criteria as either low grade or high grade.[24] Invasive neoplasia was defined as neoplastic cellular proliferation extending into the sm layer 3 or beyond (>1000 μm).[24] Early CRC was defined when intra or superficial sm carcinoma was present with no vertical extension into sm layer 3 or muscularis.[24] The histopathological specimens were then compared with HFUS and HMCC staging.

Image capture
All endoscopic procedures were digitally recorded in real time using a Macintosh G4 PC interfaced with an analogue-digital PCX 540 transducer. With the aid of Macintosh I-movie software package (for Mac OsX) the entire digital video recording of the procedure was written to non-rewritable Sony CDQ74N2 650 MB compact disks in high quality large format Quick Time Player compatible mode. Further review of the endoscopic images of each procedure was thus permitted if required.

Statistical analysis
Statistically significant differences were analysed using the χ^2 tests of independence, Fisher's exact test, the Mann-Whitney U test, and McNemar's test. A p value of <0.05 was considered statistically significant. The Bonferroni correction for multiple comparisons of data was applied where relevant. Calculations were made using the SPSS statistical package for Windows 1998 (Microsoft Corp, USA). The University of Sheffield Statistics Unit provided statistical advice and support.

RESULTS
A total of 53 patients with 53 PT type II lesions fulfilled the inclusion criteria to the study (31 males, median age 63 years (range 41–79)). One patient was excluded due to inadequate bowel preparation on two consecutive occasions. Five patients (9.6%) received conscious sedation using midazolam (median dose 2 mg (range 1–6)). Intubation to the caecum and terminal ileum was possible in 51/52 patients (98%). One patient had received a previous right hemicolectomy for Dukes' "A" carcinoma three years previously—intubation to the neoterminal ileum was achieved. There were no complications.

Table 1 Correlation between Nagata stage (tT), high frequency ultrasound (HFUS) stage (uT), and histopathological stage (pT)

Histopathology (pT)	No	Nagata stage (tT)			HFUS stage (uT)		
		sm1	sm2	sm3	sm1	sm2	sm3
pT sm1	12	9 (75%)	2	1	12 (100%)	0	0
pT sm2	13	1	8 (61%)	4	1	12 (92%)	0
pT sm3	27	10	4	13 (48%)	1	1	25 (93%)
Total	52	20	14	18	14	13	25

sm, submucosal.

Twelve PT type II lesions were located in the caecum with 13, 15, 10, and 2 lesions located in the ascending, transverse, sigmoid colon, and rectum, respectively. Histopathologically, 12 (23%) PT class II lesions were restricted to sm layer 1 with 13 (25%) and 27 (52%) involving sm layers 2 and 3, respectively. Median lesion size was 8 mm (range 2–18). EMR inclusion criteria were met by 25 (48%) lesions with the remaining 27 (52%) being referred for surgical excision. Of the 25 lesions meeting EMR inclusion criteria, eight (32%) were resected en bloc with 17 (68%) using a piecemeal approach. Cold biopsy sampling was performed in the remaining 27 lesions referred for direct surgical excision. Histological verification of lymph node status was therefore possible in 27 cases.

HMCC phase 1 T/N staging
High magnification imaging and subsequent Nagata criteria[17] were obtained in all 52 lesions. Nagata classes A, B, and C crypt patterns were observed in 9/12 (75%), 8/13 (61%), and 13/27 (48%) lesions with sm1, sm2, and sm3+ confirmed pT disease, respectively. Seventeen lesions were staged as pN0 of which 8/17 (47%) were correctly staged using the Nagata type C crypt pattern as predictive of node positive disease. HMCC over staged 9/17 (53%) lesions as tTN1 compared with the actual pN0 status at histopathology. Of the 10 lesions staged as pN1, four (40%) were predicted as tTn1 disease with six (60%) being under staged using HMCC as tTN0. Using the Nagata class C crypt pattern as a predictor of LNM yielded a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 0.31, 0.57, 0.4, and 0.47, respectively. The kappa coefficient of agreement between Nagata class C crypt and LNM was 0.25 (95% confidence interval (CI) 0.5–0.26).

HFUS phase 2 T/N staging
Acoustic coupling was achieved in all 52 lesions (48 direct water couple/four balloon assisted). Twelve lesions were assessed using HFUS (uT) as sm1, 12 sm2, and 25 sm3+. Compared with the histopathological specimens, overall accuracy for sm1, sm2, and sm3+ was 100% (12/12), 92% (12/13), and 93% (25/27), respectively. Forty nine lesions (94%) were correctly staged using HFUS compared with the histopathological specimen. Of the remaining three lesions (6%), one caecal PT II lesion was under staged as sm2 (pT sm3+/T2) with two ascending colonic PT II lesions under staged as uT sm3 compared with the pT stage of T4 disease. Using the criteria of Cho and colleagues[23] at HFUS as predictive of LNM sensitivity, specificity, PPV, and NPV were 0.8, 0.88, 0.8, and 0.88, respectively. The kappa coefficient of agreement between HFUS anticipated LNM was 0.68 (95% CI 0.4–0.97).

The prevalence of nodal disease overall was 19% (10/52), with 80% (8/10) occurring in the sm3+ group. pN0 disease was observed in 17 (63%) of PT type II lesions, of which 15 (88%) were correctly staged using HFUS. Eight lesions (8/10–80%) were staged as uTN1 that were confirmed as pN1 postoperatively. Twenty per cent (2/10) node positive lesions were however under staged at HFUS. HFUS was significantly more sensitive at predicting both T and N stage compared with HMCC (p<0.0001/p<0.001, respectively). Correlations between Nagata endoscopic stage, HFUS stage, and histopathology are summarised in tables 1 and 2.

DISCUSSION
This is the largest prospective study and the first in the UK to address the efficacy of HMCC and HFUS for T and N staging of PT type II colorectal lesions performed by a single endoscopist. These data validate the retrospective analysis of Matsumoto *et al* from Japan.[21] Our data suggest that HFUS is superior to HMCC using the Nagata crypt subanalysis[17] (conventionally considered to be the "gold standard") for both invasive depth estimation and anticipation of LNM. Furthermore, we have demonstrated a significant association between deep submucosal invasion and the presence of lymph node metastasis, as previously described by Japanese groups.[11 25]

HMCC has now been shown by both Japanese and Western groups to provide an accurate in vivo tool to distinguish between neoplastic and non-neoplastic lesions of the colorectum.[26 27] Kato *et al*'s retrospective review of 3438 lesions[28] (classified according to the modified criteria of Kudo and colleagues[13]) showed diagnostic accuracy rates of 75%, 94%, and 85% when distinguishing non-neoplastic lesions from adenoma and invasive carcinomas, respectively. However, non-specified grade of dysplasia and the use of an adapted Vienna criterion for histopathological analysis make translation of these data to Western practice difficult. Using standardised morphological, crypt pattern, and histopathological criteria, the Sheffield group subsequently demonstrated a sensitivity of 98% and specificity of 92% when distinguishing non-neoplastic from neoplastic lesions.[2] When differentiating neoplastic/non-invasive from neoplastic/ invasive disease, sensitivity was poor (50%) with a specificity of 98%.[2] Hence although providing the endoscopist with a useful tool to improve the diagnostic yield of significant lesions, while lowering the burden of insignificant histopathological sampling, it cannot be used as a complete replacement for histopathology.

Few studies have addressed the use of HMCC as an in vivo staging tool for PT type II colorectal lesions where deep

Table 2 Correlation between preoperative Nagata stage (tT), high frequency ultrasound (HFUS) (uN), and pathological findings (pN) for lymph node staging

Histopathology	No	Nagata stage (tT)		HFUS stage (uT)	
		tTN0	tTN1	uTN0	uTN1
pN0	17	8	9	15	2
pN1	10	6	4	2	8
Total	27	14	13	17	10

submucosal invasion has been associated with a higher risk of nodal disease (10–15%).[11][29] Endoscopic resection in this group is therefore potentially undesirable due to the risk of perforation (secondary to entrapment of the muscularis mucosa), non-curative excision, and untreated nodal disease.[12] Nagata et al prospectively examined the efficacy of a novel subclassification of the Kudo type V(n) crypt pattern and associated incidence of mucosal desmoplasis for PT type II lesions.[17] The incidence of sm2+ disease in this study was 38%, 94%, and 100% for Nagata classes A, B, and C, respectively.[17] However, despite this initial apparent "high accuracy" data, other prospective validation studies have failed to reproduce these findings with reported poor specificity rates (50%) and a subsequent trend to over stage lesions.[16] The use of chromoscopic colonoscopy without magnification imaging to establish discrete morphological characteristics favouring sm2+ disease has been described by one other group.[30] Using the criteria of Saitoh et al (expansion appearance, present; surface depression, deep; irregularity of depressed surface, uneven; and converging fold toward the tumour) sensitivity and specificity rates were 90%.[30] A fall in specificity to 70% was however observed when lesions reported as "intramucosal" carcinoma were excluded from the analysis.[30] Thus as the Nagata class C crypt[17] was the most commonly observed invasive pattern in our study we would suggest that Nagata C be adopted as an indication for subsequent HFUS imaging rather than an alternative staging modality.

Previous studies from Japan have reported the efficacy of TTS HFUS for invasive depth estimation in PT type II colorectal lesions. Saitoh et al in a prospective analysis of 49 PT type II lesions using a 20 MHz TTS mini probe established diagnostic radial imaging in 76% of cases.[20] Overall accuracy of invasive depth using 20 MHz HFUS was 88% (43/49) (with reference to sm3 and the muscularis mucosa), 85% (11/13) for sm1 carcinoma, and 100% (3/3) for intramucosal carcinoma.[20] However, invasive depth was incorrectly determined in 12% (6/49) of lesions.[20] This occurred in three cases due to insufficient acoustic coupling and in two cases due to an attenuated scanning range caused by an elevated G-type lesion morphology.[20] Furthermore, regional nodal disease was not established due to the limited depth of penetration using 20 MHz imaging.

In our study, acoustic coupling was achieved in all 52 (100%) lesions with four (7%) requiring the balloon assistance technique of Tseng and colleagues.[22] This may in part account for the improved scanning rates in our series. However, when comparing "adjusted" HFUS imaging (excluding failed acoustic coupling), the overall accuracy rate for invasive depth estimation in our cohort was similar to those of Saitoh and colleagues[20] and Tsuruta and colleagues[31] (94%, 88%, and 88.9%, respectively).

Other studies have addressed the potential role of HFUS for nodal staging of colorectal carcinoma.[32][33] HFUS imaging (12.5 MHz, using the criteria of Cho and colleagues[23]) to predict LNM in our series had a sensitivity of 0.8 with an NPV (lymph node negative prediction) of 0.88, data comparable with that of Tseng and colleagues,[22] Hamada and colleagues[34] and Hunerbein and colleagues.[35] However, Stergiou et al have reported lower sensitivity rates (56%) compared with other groups.[33] In this series, 4/9 pN1 lymph nodes were not detected using HFUS.[33] Many reasons may account for the disparity in these data, including recently improved acoustic coupling using the Tseng balloon technique,[22] operator dependent error, and the limited tissue penetration resultant from higher frequency imaging.

There are limitations to our study. All HMCC and HFUS imaging was performed by a single endoscopist. The absence of a "blinded" single centre and operator design may therefore introduce bias error. Hence application of these data to current clinical practice requires further validation using a prospective, randomised, double blind, multicentre study design.

In conclusion, our data provide more evidence to suggest that TTS HFUS imaging is presently the most sensitive and specific tool for establishing both invasive depth and the presence of LNM for PT type II colorectal neoplasia. We have shown HFUS to be superior to HMCC alone (using modified Nagata criteria[17]). However, our data suggest that HMCC may be complimentary to HFUS and provide important endoscopic criteria for further ultrasound imaging. Clinically, this is of paramount importance when selecting lesions suitable for endoscopic mucosal resection as opposed to surgical resection.

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EDITOR'S QUIZ: GI SNAPSHOT ....

Answer

From question on page 1572

Upper gastrointestinal endoscopy showed polypoid masses (fig 1). There were multiple large polypoid lesions distributed throughout the body, fundus, and cardia of the stomach, with characteristic antral sparing. Endoscopic ultrasound demonstrated diffuse and regular gastric wall thickening of the second layer, corresponding to the mucosa (between the arrows in fig 2) with preservation of wall stratification. A full thickness gastric mucosal biopsy revealed foveolar hyperplasia with cystic dilation (fig 3). The pathological diagnosis was Menetrier's disease.

Menetrier's disease (hypertrophic protein losing gastropathy) is a rare clinical entity of unknown aetiology. It is characterised by giant gastric folds associated with epithelial hyperplasia.[1] A polypoid variant of Menetrier's disease has been described that resembles multiple hyperplasic gastric polyps. Menetrier's disease is typically associated with protein losing gastropathy and with hypochlorhydia. Patients may present with weight loss, epigastric pain, vomiting, anorexia, oedema, and haematemesis. Of the 200 cases of Menetrier's disease reported in the literature, 30 (15%) have been associated with carcinoma.[2] Ideal treatment of hyperplasic gastropathy is unclear. In patients not responding to medical therapy, partial or total gastric resection is reserved for severe complications, such as refractory or recurrent bleeding, obstruction, severe hypoproteinaemia, or cancer development. The differential diagnosis for the endoscopic appearances includes lymphoma, Zollinger-Ellison syndrome, amyloidosis, eosinophilic gastritis, and infiltrative neoplastic entities.

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