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Title Page

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MRI for local staging of colon cancer; can MRI become the optimal staging modality for colon cancer patients?

2. Short title;
Colon cancer staging: MRI or CT?

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Structured abstract

Background
Currently colon cancer is staged with computed tomography (CT). However, magnetic resonance imaging (MRI) is superior in the detection of colorectal liver metastasis and MRI is standard in local staging of rectal cancer. Optimal (local) staging of colon cancer could become crucial in selecting patients for neo-adjuvant treatment in the near future (FOXTROT trial).

Objective
The purpose of this study was to evaluate the diagnostic performance of MRI for local staging of colon cancer.

Design
Retrospective study.

Settings
Study Conducted at our institute.

Patients
In total 55 patients with biopsy proven colon carcinoma were included.

Main outcome measures
All patients underwent a MRI (1.5 Tesla; T2 and diffusion weighted imaging) of the abdomen and were retrospectively analysed by two blinded, independent readers. Histopathology after resection was the reference standard.
Both readers evaluated tumor characteristics being; invasion through bowel wall (T3/T4 tumors), invasion beyond bowel wall of ≥5mm and/or invasion of surrounding organs (T3cd/T4), serosal involvement, extramural vascular invasion and malignant lymph nodes(N+). Inter-observer agreement was compared using Kappa (κ) statistics.

Results
MRI had a high sensitivity (72-91%) and specificity (84-89%) in detecting T3/T4 tumors (35/55) and a low sensitivity (43-67%) and high specificity (75-88%) in detecting T3cd/T4 tumors (15/55). For detecting serosal involvement and extramural vascular invasion MRI had a high sensitivity and moderate specificity and a moderate sensitivity and specificity in the detection of nodal involvement. Interobserver agreements were predominantly good, the more experienced reader achieved better results in the majority of these categories.

Limitations
Retrospective nature of study and moderate number of inclusions.

Conclusion
MRI has a good sensitivity for tumor invasion through the bowel wall, extramural vascular invasion and serosal involvement. Additionaly, together with its superior liver imaging, MRI might become the optimal staging modality for colon cancer. However, more research is needed to confirm this.

Keywords
1. Colon cancer
2. Screening
3. Imaging
4. Gastroenterology
5. Medical oncology
6. Radiology

Introduction

Distant and local staging of colon cancer is currently mainly performed with computed tomography (CT). However, according to a recent meta-analysis CT has a limited sensitivity of 75% for detecting liver metastasis[1].

At diagnosis, 15-23% of colorectal cancer (CRC) patients have liver metastasis[2, 3]. Detection is crucial because it means poor prognosis and a different clinical approach and treatment[4]. Multiple studies already demonstrated that magnetic resonance imaging (MRI) is superior to CT for the detection of liver metastasis[1, 5]. Both the introduction of diffusion-weighted imaging (DWI) and the use of liver-specific hepatobiliary contrast agents have contributed to the superior results of MRI in detecting small liver lesions[6, 7].

Unlike in rectal cancer where local staging with imaging is crucial to determine the proper (neoadjuvant) treatment strategy, imaging in colon cancer is mostly used as a surgical roadmap. However, the role of imaging for local staging of colon cancer might emerge in the near future; several small studies and case reports showed additional value of neo-adjuvant treatment in locally advanced colon cancer[8-12]. Furthermore, a large multicenter study, FOXTROT[13], is currently investigating the benefits of neo-adjuvant chemotherapy for patients with locally advanced colon cancer. If the FOXTROT trial confirms initial promising reports, neoadjuvant treatment in colon cancer patients will be adopted as standard therapy, just like in rectal cancer patients. If so, preoperative imaging will become a crucial tool to select patients for neo-adjuvant treatment. In the FOXTROT trial, CT is used to detect locally advanced colon cancer and thus eligibility for neo-adjuvant treatment. Nonetheless a recent meta-analysis[14] showed disappointing results for staging colon cancer with CT. In our opinion this means other modalities such as MRI should be at least considered. MRI is well established in local staging of rectal cancer due to its superior results compared to CT[15]. However, little is known about the local staging of colon cancer with MRI. If MRI is able to accurately stage colon tumors, it might be the ideal imaging tool for simultaneous local and distant staging. Therefore, the aim of this study was to evaluate the diagnostic performance of MRI for local staging of colon cancer patients.

Materials and methods

This study was approved by the institutional review board. Informed consent was waived because of the retrospective nature of the study.

Patient population

Eighty consecutive patients were diagnosed with colon cancer at [blinded] from April 2014 until May 2015. Inclusion criteria were as follows: (a) biopsy-proven adenocarcinoma of the colon (with a distal tumor margin > 15 cm from the anorectal junction, measured at endosccopy), (b) preoperative staging with MRI, (c) availability of histopathological results after surgical resection of the colon. Twenty-five patients were excluded for the following reasons: no surgical resection (only a polypectomy with tumor free margin was performed during colonoscopy n=11), inoperable disease (n=8), benign outcome (e.g. adenoma, these patients received a MRI before the definitive histopathological result was available) at histopathology (n=5) and insufficient MR image quality due to severe motion artefacts (n=1). This left a total of 55 patients that met the final inclusion criteria.

MR imaging protocol

Imaging was performed with a 1.5T MRI (Ingenia**,** Philips Medical Systems, Best, The Netherlands) using a phased array body coil. Patients were placed in feet first supine position. Bowel preparation consisted of ≥ 3 hour fasting before the MR examination. To minimize peristaltic movements, patients received an intravenous bolus injection before the MR examination, of 20 mg Hyoscine Butylbromide (Buscopan®, Boehringer Ingelheim BV, Ingelheim, Germany) before the start of the MR examination, or 1mg of glucagon (GlucaGen® Novo Nordisk, Bagsværd, Denmark) in case of a contra-indication to receive Hyoscine Butylbromide. The scan protocol consisted of a MR liver protocol combined with an additional MR colon protocol covering the whole abdomen. This additional colon protocol consisted of T2-weighted turbo spin echo (TSE) sequences (2 axial stacks and 1 coronal stack), an axial diffusion-weighted sequence (acquired in 3 stacks; b1000 being the highest b-value) and a pre- and post-contrast T1 Thrive sequence (in coronal plane). The echo time (TE) and repetition time (TR)

were 80ms and 5596ms for T2 and 65ms and 3808ms for DWI respectively. The slice thickness for T2 and DWI was 3mm and 8mm respectively. The minimal slice gap for T2 and DWI was 3mm and 0mm respectively. Field of view of 390 x 390 mm for T2 and 380 x 290 mm for DWI. Acquisition matrix for the T2 and DWI was 392 x 392 and 152 x 115 with an acquisition voxel size (mm) of 0.99 x 0.99 x 3.00 and 2.50 x 2.51 x 8.00 respectively. The number of excitations (NEX) were 2 for T2 and 4 for DWI. Acquisition time of the MR colon protocol was 18 minutes. Total acquisition time of the colon + liver protocol was 50 minutes.

Image Evaluation

Two readers (reader 1 with 12 and reader 2 with 8 years experience in reading abdominal MRI) independently assessed the MR colon images to evaluate the local tumor status. The liver images were used for further clinical staging of distant metastases (outside the scope of this study). The readers were blinded for the surgical outcome and histological results. Both readers scored the following items: [1] location of the tumor (caecum, ascending colon, transverse colon, descending colon and sigmoid);[2] tumor stage (T1-2 vs T3-4); [3] in case of a T3 or T4 tumor, the depth of extramural invasion (EMD), an EMD of ≤5mm was classified as a T3ab tumor and an EMD of >5mm was classified as a T3cd tumor. [4] in case of a T4 tumor: the presence of serosal involvement and/or adjacent organ invasion; [5] extramural venous invasion (EMVI); and [6]lymph nodes status (N0/N+). The readers evaluated the abovementioned items by use of a confidence level score; 0 = definitely not, 1 = probably not, 2 = uncertain, 3 = probably yes, 4 = definitely yes). All imaging datasets (T2-weighted, DWI, non-enhanced and contrast-enhanced Thrive) were at the readers' disposal.

Image assessment criteria

The criteria used for determining the T-stage were based on the AJCC 5th TNM-classification, because this edition is still used in [blinded] and other European countries (e.g. United Kingdom). For positive nodal involvement the criteria were a short axis diameter of 8 mm or more and/or a cluster of 3 or more lymph nodes with a short axis diameter of >5 mm. Extramural venous invasion (EMVI)

was defined as direct invasion of the tumor in a vascular structure, serpiginous vessels and/or irregular aspect of vessel wall near the tumor site[16].

Statistical analyses

Descriptive statistics were used for the assessment of baseline characteristics. For diagnostic performance the following outcomes were evaluated: T-stage (T1/T2 vs T3/T4 and T1-T3ab vs T3cd/T4), serosal involvement, EMVI and nodal involvement. The diagnostic performance of MRI for the abovementioned outcomes was evaluated by means of receiver operator characteristics (ROC) curves for which areas under the ROC curve (AUC) with 95% confidence intervals were calculated. Sensitivity, specificity with 95% confidence intervals were calculated by 2x2 contingency tables based on the confidence level scores. Cut-off for confidence level scores was set between 2 and 3 before the onset of the study. Analyses were performed with SPSS® software version 22.0 (IBM corporation, Armonk, New York, U.S.A). Inter-observer agreement was compared using quadratic weighted kappa statistics and was categorized as poor agreement, fair, moderate, good and very good agreement according to kappa (κ) values <0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80 and 0.81-1.00, respectively.

Reference standard

Surgery was performed using standard techniques[17]. The resected specimens were processed using standard histologic protocol[18]. All specimens were evaluated by a senior pathologist with 10 years of experience in gastrointestinal pathology.

Results

Patient and tumor characteristics

The final study population consisted of 55 patients (23 female, 32 male) with a median age of 69 years (range: 34–84 years). On average, surgery was performed 22 days (range of 3-51 days) after the staging MRI. In 50 out of 55 patients ≥12 lymph nodes were harvested. In 5 patients <12 lymph nodes were harvested with a minimum of 6 resected lymph nodes. A tumor free resection margin (i.e. R0 resection) was achieved in all of the included patients.

Detailed tumor characteristics are given in Table 1.

Diagnostic performance of MRI

The results as stated below are summarized in table 2 and ROC curves results are presented in table 3.

Tumor location

Both readers correctly identified the location of the tumor in each patient. Ten tumors were located in the caecum, fifteen in the ascending colon, three in the transverse colon, seven in the descending colon and twenty in the sigmoid. Interobserver agreement between both readers was perfect (κ=1.0).

Tumor stage

Area under the curve (AUC) for differentiating between T1-2 and T3-4 tumors was 0.88 (95%CI 0.77-0.99) for reader 1 and 0.85 (95%CI 0.74-0.96) for reader 2. The sensitivity and specificity for detecting T3-T4 tumors were 91% (95%CI 76-98%) / 84% (95%CI 60-96%) for reader 1 and 72% (95%CI 50-87%) / 89% (95%CI 65-98%) for reader 2. In patients with a T3 tumor, the sensitivity and specificity for detecting T3cd/T4 tumors were 40% (95%CI 17-67%) and 88% (95%CI 65-98%) for reader 1 and 60% (95%CI 33-83%)and 75% (95%CI 58-87%) for reader 2.

Interobserver agreement between both readers was good (κ=0.72) for the differentiation between T1-2 vs T3-4 tumors, and moderate (κ=0.55) for the differentiation of T3cd/T4 tumors.

Serosal

The AUC for detecting serosal involvement was 0.88 (95%CI 0.78-0.98) for reader 1 and 0.72 (95%CI 0.51-0.93) for reader 2. The sensitivity and specificity for detecting serosal involvement were 88% (95%CI 47-99%)/74% (95%CI 59-86%) for reader 1 and 68% (95%CI 43-86%)/64% (95%CI 46-79%) for reader 2 (table 2).

Interobserver agreement between both readers was good (κ=0.62).

Nodal status

The sensitivity and specificity for detecting nodal involvement (N0 versus N+) were 47% (95%CI 25-71%)/86% (95%CI 70-95%) for reader 1 and 68% (95%CI 43-86%)/64% (95%CI 46-79%) for reader 2 (table 2).
Interobserver agreement between both readers was moderate (κ=0.60).

Extramural venous invasion

The AUC for detecting EMVI was 0.77 for both readers (95%CI 0.63-0.91 for reader 1 and 0.63-0.92 for reader 2). Both readers had a high sensitivity of 100% (95%CI 60-100%) and 88% (95%CI 47-99%) and a moderate specificity (62% (95%CI 46-75%) and 70%(95%CI 55-82%) in detecting EMVI respectively.
Interobserver agreement between both readers was moderate (κ=0.60).

Discussion

The aim of this study was to evaluate the diagnostic performance of MRI for local staging of colon cancer patients. Our findings show that MRI is able to accurately detect tumors with invasion through the bowel wall. In addition, MRI shows promising results for more recently adopted risk factors such as serosal involvement and EMVI. This means that, together with the already known superior results for the detection of small liver metastasis, MRI could become the most optimal local and distant staging modality for colon cancers.

MRI showed accurate results in detecting tumor invasion through the bowel wall, with a high sensitivity and specificity (Table 2). Especially the specificity seems higher compared with a recent meta-analysis[14] on staging of colon cancer with CT, where the summary sensitivity and specificity estimates for detecting tumor invasion beyond the bowel wall (T3-T4) with CT were 90% and 69% respectively, it should be noted however, the 95% confidence intervals do overlap for both the sensitivity and specificity (table 4[14, 19-21]). The seemingly higher specificity of MRI for colon cancer can probably be explained by the superior soft tissue contrast of MRI. Only one study is comparable to ours in this category, it is a very recent study by Hunter et al.[19] which demonstrated a lower sensitivity and specificity compared with our results (Table 4). This means that

more research is needed to define the role of MRI for colon cancer staging. Although it is not the focus of our study, diffusion weighted imaging (DWI) was especially useful for locating the colon tumor (as shown in figure 1A). The high signal on DWI made it easier to detect small colon tumors.

The detection of T3cd/T4 tumors remains a problem with MRI. In our study, the low sensitivity (40-60%) indicates that the EMD is mainly underestimated and therefore T3cd/T4 tumors are understaged, possibly due to microscopic tumor expansion, which is not detectable with MRI.
Disappointing results in detecting T3cd/T4 tumors were also found for CT in a recent meta-analysis[14] with a higher summary sensitivity but lower specificity estimates compared with our results (Table 4). These low summary estimates might be caused by desmoplastic reaction being interpreted as tumor expansion, resulting in overstaging. A recent study by Rollven et al.[20] conducted with MRI and CT, and scored by 2 observers, showed a higher sensitivity and specificity for both modalities with MRI being superior (Table 4). However, this study was relatively small (n=29) and was carried out by two very experienced observers (both dedicated abdominal radiologist with 6 and 18 years experience). In contrast, the study by Hunter et al. (which included 55 patients who received MRI only) shows much lower sensitivity and specificity compared to the results presented by Rollven et al. and our study (Table 4). Hence, further research is needed to fully understand the role of imaging for the detection of EMD.

According to our results MRI has a good accuracy in detecting serosal involvement (AUC=0.85-0.88). The ability of MRI to rule out serosal involvement could provide clinicians with valuable information concerning operability and prognosis. Patients with serosal involvement (figure 1B) have a poorer five-year survival (24.3%) than those in whom it is absent (55.4%)[22]. The mediocre specificity could be explained by desmoplastic reaction involving the serosa or fascia, which may erroneously be interpreted as tumor expansion. To our knowledge there is no literature about the accuracy of CT in the detection of serosal involvement as defined in our study.

Results for detecting nodal involvement were mediocre for both readers. According to a recent meta analysis[14], CT shows comparably disappointing results, with summary estimates for sensitivity and specificity of 71% and 67% respectively. In the pilot study for the FOXTROT trial (using CT) the accuracy was also disappointing with a good sensitivity of 83% but a low specificity of 44%[13]. CT and MRI both seem unreliable in the detection of nodal involvement[19, 20]. This fact is also well known in staging of rectal cancer[23]. Although lymph nodes are clearly visible diffusion weighted images (as shown in figure 1C), this does not necessarily represent metastatic involvement, as the high cellularity in lymph nodes causes a high DWI signal in benign lymph nodes as well[24, 25]. Several factors contribute to this low accuracy. Lymph node diameter is the most commonly used criterion but is not accurate for assessing lymph node metastasis in colon cancer[26]. Moreover, false negative results are caused by microscopic metastasis in lymph nodes with a normal diameter and false positive results are caused by benign lymph nodes that are enlarged due to inflammation. This is an important diagnostic problem, because distant nodal involvement along the mesenteric arteries may justify a more extensive hemicolectomy. Interestingly, new intravenous contrast agents such as gadofosveset show promising results for nodal staging in rectal cancer[27]. Further research is warranted because this may improve the detection of nodal involvement in colon cancer patients.

In detecting EMVI, our results show a very high sensitivity. The ability of MRI to rule out EMVI provides clinicians with valuable information, because EMVI results in a poorer five-year survival (25.0%) than if EMVI is absent (57.4%)[22]. A recent large study[21], which used CT to detect EMVI, described a low sensitivity and mediocre specificity (Table 4). Furthermore the study by Rollven et al. [20] confirms the superior accuracy of MRI for EMVI while the study by Hunter et al.[19] reports a low sensitivity with a good specificity (table 4). Nonetheless it seems MRI is superior in the detection of EMVI. The specificity in our study was mediocre, which could be explained by traction on the vessels and/or thrombus formation due to altered hemodynamics caused by local inflammation, however this theory needs to be confirmed by other studies.

Both readers have experience with reading MRI of the abdomen especially MRI of the rectum, however reader 1 has a four years advantage and is more accurate in the majority of the categories (table 2). It seems experience does translate into better results however it should be noted that this difference is minor in most categories and the interobserver agreement was at least moderate in all categories.

Limitations

Our study has some limitations. Firstly, the retrospective nature of this study. Secondly, a total number of 55 patients were included in this pilot study. Large multicenter trials are needed to define the role of MRI for dedicated colon staging.

Clinical impact

Compared to previous literature on CT our study shows that MRI seems to perform as well as CT in local staging, with the added benefit that it has the potential to be more accurate in detecting prognostic factors such as EMVI. An additional important advantage of MRI is its superiority in detecting small liver metastases with the evaluation of the colon tumor in one imaging session[1]. The most recent EURECCA expert guidelines advise MRI of the liver[28] in the preoperative staging of colorectal cancer. This would mean that the MR sequences for local staging of the colon tumor can be performed in the same MR imaging session of the liver. This combined approach could result in the most optimal abdominal staging tool for colon cancer patients. Another advantage of this approach is the avoidance of ionizing radiation and nephrotoxic contrast agents.

Conclusion

Our study shows that MRI has the potential to become a valuable tool in preoperative staging of colon cancer, with results that are comparable to CT in the detection of important prognostic factors such as tumor and nodal staging. In addition, MRI seems to have a high sensitivity for additional risk factors, such as serosal involvement and EMVI. Combined with its known superiority in

detecting liver metastasis, MRI could become the most optimal abdominal staging method for colon cancer patients. However, due to the limited research on this topic, more research is needed to confirm these promising results.

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Figure and table legend

Figure 1A.
T2 weighted sequence (left) and corresponding b1000 diffusion-weighted images (right), show a small T2 tumor in the ascending colon (arrow). This small tumor could easily be missed on T2-weighted images. However it is clearly depicted on diffusion weighted images.

Figure 1B.
T2 weighted image of a patient with a tumor of the ascending colon (arrow). The tumor grows through the bowel wall. Both readers accurately identified the serosal involvement (black arrowheads), which was nicely depicted with MRI and the tumor was staged as a T4 tumor. This was confirmed by histopathology.

Figure 1C.
T2 weighted sequence (left) and corresponding b1000 diffusion-weighted imaging (right) show an example of a small T3 tumor in the ascending colon (arrowhead) and local, enlarged lymph nodes (arrows). Note the conspicuity of these lesions on DWI, aiding in the detection of the tumor and lymph nodes.

Table 1.
Patient and tumor characteristics. Asc. Colon = Ascending colon, Colon Tr. = Colon transversum, Des. Colon = Descending colon.

Table 2.
Study results. Serosa +/- = detection of serosal involvement. N +/- = detection of nodal involvement. EMVI +/- detection of extramural vascular involvement. Sens.=sensitivity, Spec.=specificity. The numbers between the brackets represent the 95% confidence interval (CI).

Table 3.
Receiver operating characteristic (ROC) curves results. AUC = Area under the curve as measured with a ROC curve. The numbers between the brackets represent the 95% confidence interval (CI). Serosa +/- = detection of serosal involvement. N +/- = detection of nodal involvement. EMVI +/- detection of extramural vascular involvement.

Table 4.
Overview of comparable studies and results. The numbers between the brackets respresent the 95% confidence intervals. *This meta-analysis presents the accuracy for staging of colon cancer with computed tomography (CT), and included both the studies by Rollven[20] et al. and Dighe[21] et al. except for EMVI which is given separately.

Table 1

Patient gender	**Female**	**Male**			
	23	32			
Patient age	**Median**	**Range**			
	69 years	34-84 years			
Tumor location	**Caceum**	**Asc. Colon**	**Colon Tr.**	**Des. Colon**	**Sigmoid**
	10	15	3	7	20
Tumor stage	**T1**	**T2**	**T3ab**	**T3cd**	**T4**
	4	15	19	9	8
Serosal inv.	**negative**	**positive**			
	47	8			
Nodal stage	**N0**	**N+**			
	36	19			
EMVI	**negative**	**positive**			
	38	17			
Time between MRI and surgery	**Average**	**Range**			
	22 days	3-51 days			

Table

Table 2

	Reader 1		Reader 2	
Tumor stage	**Sens.**	**Spec.**	**Sens.**	**Spec.**
T1/T2 vs T3/T4	91% (76-98%)	84% (60-96%)	72% (50-87)	89% (65-98)
T1-T3ab vs T3cd/T4	40% (17-67%)	88% (73-95%)	60% (33-83%)	75% (58-87%)
Serosa +/-	88% (47-99%)	74% (59-86%)	75% (36-96%)	72% (57-84%)
Nodal stage +/-	47% (25-71%)	86% (70-95%)	68% (43-86%)	64% (46-79%)
EMVI +/-	100% (60-100%)	62% (46-75%)	88% (47-99%)	70% (55-82%)

Table 3

	Reader 1	Reader 2
Tumor stage	**AUC**	**AUC**
T1/T2 vs T3/T4	0.88 (0.77-0.99)	0.85 (0.74-0.96)
Serosa +/-	0.88 (0.78-0.98)	0.72 (0.51-0.93)
Nodal stage +/-	0.73 (0.58-0.88)	0.63 (0.47-0.80)
EMVI +/-	0.77 (0.63-0.91)	0.77 (0.62-0.92)

Table 4

Modality	T3-T4		T3cd-T4		N+		EMVI	
MRI	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Hunter et al.[19]	74% (60-85%)	58% (32-81%)	67% (45-83%)	79% (63-90%)	26% (13-46%)	81% (64-91%)	63% (41-81%)	80% (64-90%)
	42% (28-57%)	83% (55-95%)	43% (24-63%)	94% (81-98%)	35% (19-55%)	74% (57-86%)	26% (12-49%)	91% (78-97%)
Rollven et al.[20]	N/A		77% (50–92%)	100% (81-100%)	86% (49–97%)	68% (47–84%)	75% (41–93%)	84% (62–95%)
			92% (67–99%)	94% (72–99%)	86% (49–97%)	64% (43–80%)	75% (41–93%)	79% (57–92%)
our results	91% (76-98%)	84% (60-96%)	40% (17-67%)	88% (73-95%)	47% (25-71%)	86% (70-95%)	100% (60-100%)	62% (46-75%)
	72% (50-87%)	89% (65-98%)	60% (33-83%)	75% (58-87%)	68% (43-86%)	64% (46-79%)	88% (47-99%)	70% (55-82%)
CT								
Nerad et al.*[14]	90% (83-95%)	69% (62-75%)	77% (66-85%)	70% (53-83%)	71% (59-81%)	67% (46-83%)		
Rollven et al.[20]							38% (14– 69%)	95% (75–99%)
							38% (14-69%)	79% (57–92%)
Dighe et al.[21]							47% (32-63%)	68% (56-79%)

Figure1

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