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Colonic transit in patients after anterior resection: prospective, comparative study using single-photon emission CT/CT scintigraphy

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Title: A prospective, comparative study of colonic transit using SPECT / CT scintigraphy in patients after anterior resection

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- Dr Kheng-Seong Ng was involved in study conception and design, patient recruitment, data collection, analysis and interpretation and writing and reviewing the final manuscript.
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ABSTRACT

Background:

Bowel dysfunction following anterior resection (AR) is well documented, but its pathophysiology remains poorly understood. No studies have assessed whether postoperative variation in colonic transit contributes to symptoms. This study measured colonic transit using planar scintigraphy and SPECT/CT in patients following AR, stratified according to postoperative bowel function.

Methods:

Planar and SPECT scintigraphy was performed on 50 randomly-selected AR patients (37M, mean 72.3yrs [SD9.0]). Symptoms were assessed using the 'low anterior resection syndrome' (LARS) score. Following gallium-67 ingestion, scintigraphy was performed at pre-defined time-points. Nine 'regions-of-interest' were defined and the following measured/calculated: (i) geometric centre (GC); (ii) percentage isotope retained; (iii) GC 'velocity'; and (iv) colonic half-clearance time ($T_{1/2}$). Transit parameters were compared in subgroups of patients according to their LARS score using ROC-curve analyses.

Results:

Overall, 17 patients had 'major-LARS', 9 had 'minor-LARS', and 24 had 'no-LARS'. Compared with 'no-LARS', 'major-LARS' patients had significantly different transit profiles: at 32 hours, (i) GCs were greater (median 5.94 [range 2.35–7.72] vs. 4.30 [2.12–6.47], $P=0.015$); (ii) 'percentage-retained' was less (median 53.8% [SEM6.5] vs. 89.9% [3.4], $P=0.002$); (iii) GC velocities were greater (1.70 [1.18–1.92] vs. 1.45 [0.98–1.80], $P=0.013$); and (iv) $T_{1/2}$ were shorter (38.3hrs [17.0–65.0] vs. 57.0 [32.1–160], $P=0.003$). Percentage-retained at 32hrs best discriminated 'major-LARS' from 'no-LARS' (AUC 0.828).

Conclusions:

Patients with major-LARS had accelerated colonic transit compared to patients no-LARS, and this may help explain post-operative bowel dysfunction in such patients. The percentage tracer retained at 32 hours had the greatest AUC value in discriminating such patients.

Keywords:

Anterior resection syndrome; bowel dysfunction; colonic transit; scintigraphy; SPECT

INTRODUCTION

Partial/complete rectal (anterior) resection (AR) **remains** the mainstay of treatment for rectal cancer¹. It has been recognised, however, that a substantial proportion of patients who undergo AR will experience post-operative bowel dysfunction, **termed ‘anterior resection syndrome’ (ARS)**²⁻⁶, that **negatively impacts** on post-operative quality of life⁷. Despite much interest, the exact pathophysiological mechanisms underlying ARS remain poorly understood. Most studies to date have focussed on changes in ano-(neo-)rectal function, particularly the impact of surgery on sphincter integrity/function^{8, 9} and neorectal capacity/compliance¹⁰⁻¹⁵. More recently, attention has been given to possible changes in colonic motility following AR¹⁶. Such changes may arise from sympathetic denervation of the left colon following ligation of the inferior mesenteric artery during surgery¹⁷. However, no studies have robustly investigated the impact of AR on colonic motility, with previous studies being limited to case reports of colonic manometry, one of which demonstrated a reduction in contractile segmental activity and an increase in high-amplitude propagated contractions following surgery compared with healthy subjects¹⁸.

Currently, several methods exist in clinical practice to investigate colonic motility, but measurement of colonic transit is particularly useful as it provides an indication of ‘luminal movement’ through the colon rather than just myoelectrical/contractile activity¹⁹. Further, colonic transit is most accurately assessed using scintigraphy, which is regarded as the gold standard due to its superior ability to discern segmental variations in transit profiles^{20, 21}. Traditionally, the clinical utility of colonic scintigraphy is in the objective identification of delayed or ‘slow’ transit in patients with chronic constipation²²⁻²⁴, but it has also been used to identify *accelerated* transit in patients with carcinoid diarrhoea²⁵ and irritable bowel syndrome²⁶. Accordingly, measurement of colonic transit following

AR may help determine whether the symptom complex characterised by faecal urgency and frequency reflects accelerated colonic transit in such patients.

Measurement of colonic transit involves calculation of percentage activity of ingested radioisotope within different 'regions of interest' (ROI) around the colon and rectum at various time points. These ROIs are created based on the presumed anatomical location of the colon and rectum, as planar scintigraphic analysis of isotope activity using a gamma camera does not provide detailed spatial resolution of colorectal anatomy. Given the likelihood of altered colo-(neo-)rectal anatomy postoperatively, alternative imaging with superior spatial resolution is required to assure accurate creation of ROIs around the colon and (neo-)rectum and transit measurement. To this end, single photon emission computed tomography (SPECT) provides more precise spatial resolution and enhanced three-dimensional appreciation of anatomical structures and has been used to image the brain²⁷, heart²⁸, and lungs²⁹, particularly when images are hybridised with computed tomography (CT) images acquired synchronously³⁰⁻³².

Therefore, the aim of this study was to measure colonic transit using both standard planar scintigraphy and SPECT/CT in patients following AR stratified according to postoperative bowel function, in an attempt to identify postoperative variations in the transit profiles in these patient groups.

METHODS

Study Population:

The study population comprised 50 randomly-selected patients following AR, who had undergone surgery for adenocarcinoma of the distal colon or rectum at a tertiary-referral Colorectal Unit in Sydney, Australia (2002–2012) and who were without a stoma at the time of study. Notably, all patients underwent full mobilisation of the splenic flexure and high ligation of the inferior mesenteric artery and appropriate mobilisation of the rectum in the extrafascial TME plane to facilitate (at least partial) resection of the rectum, irrespective of tumour location in the hindgut. This sample was randomly selected using a random number generator (SPSS version 21; SPSS Inc., Chicago, IL, USA), from a larger cohort of 338 consecutive patients who underwent AR during the same time period. Random selection of the sample included in the present study was stratified according to the distribution of patients with ‘major LARS’, ‘minor LARS’, and ‘no LARS’ in the population of postoperative patients to prevent potential over- or under-sampling of certain groups of patients. No other exclusions were applied to the sample population. This study was approved by the Sydney Local Health District Human Research Ethics Committee (HREC/12/CRGH/203).

Clinical assessment of bowel symptoms by self-administered questionnaire:

Clinical assessment of bowel symptoms was performed using a self-administered questionnaire. Bowel function was assessed objectively using the low anterior resection syndrome (LARS) score³³ which has been validated as a robust clinical tool to quantify severity of bowel dysfunction following AR. Patients were classified as having ‘major LARS’ (scores 30 to 42), ‘minor LARS’ (scores 21 to 29), and ‘no LARS’ (scores 0 to 20). Pertinent clinico-pathological information for patients were extracted from their medical records.

Planar Scintigraphy

Bowel medications were withheld 5 days prior to the beginning of the study and were avoided until study completion. Patients remained on their normal diet throughout the study. On the morning of day 1 (time zero), 10 MBq Gallium-67 citrate (^{67}Ga -citrate, Global Medical Solutions, Arncliffe, NSW, Australia) was ingested orally mixed with 100mL water (equivalent to an effective whole-body dose of 0.7–1.0 mSv³⁴). Planar (anterior and posterior) abdominal images were acquired using a dual-head large-field-of-view gamma-camera equipped with medium-energy collimators (GE Healthcare; General Electric, Silverwater, NSW, Australia). Images were acquired serially at 3, 6, 24, 32, 48, 72, and 96 hours according to standard acquisition protocol.

SPECT/CT Scintigraphy

In addition to planar images, SPECT/CT images of the abdomen and pelvis were obtained on three separate time points: 6, 24, and 32 hours. These SPECT/CT images were acquired using a hybrid gamma camera / CT scanner that is composed of a dual-head variable angle gamma camera and a 16-slice CT scanner (GE Healthcare; General Electric Discovery 670). This hybrid scanner is designed to facilitate precise anatomical localisation of radiopharmaceutical uptake, with acquired SPECT and CT images co-registered in the same session³⁰. Specifically, SPECT images were acquired over 360° (180° per head with 60 views at 3° angle steps, 20 seconds per step) and CT images with slice thickness of 3.75 millimetres and fused SPECT/CT images were then viewed using a three-dimensional (3D) image analysis software (3D slicer, version 4.3.1; www.slicer.org).

Data processing: defining ‘regions of interest’

A variable ROI program was employed to quantify colonic transit. Due to the post-surgical anatomy of the **patients**, nine ROIs (Figure 1) were defined (as opposed to previously-described five³⁵ or seven³⁶ ROI programs used in patients with ‘native’ colonic anatomy), of which 7 were colo-(neo)rectal (regions 1-7):

- Region 0: ‘Pre-colon’, Proximal to the colon i.e. small bowel;
- Regions 1 and 2: comprised of the ascending colon (AC) divided equally into two ROIs, i.e. AC-1 and AC-2;
- Regions 3 to 6: comprised of that portion of colon between the hepatic flexure and neorectum (i.e. transverse and descending colon [TDC]), divided equally into four ROIs, i.e. TDC 1 to 4;
- Region 7: comprised of the neorectum (NR), defined as that portion of large bowel deep to the pelvic inlet; and
- Region 8: excreted faeces.

These nine ROIs were defined on both planar and SPECT images. However, given the need to appreciate the three-dimensional configuration of colonic anatomy, ROIs were drawn *first* within the SPECT images and this anatomical knowledge in turn informed drawing of ROIs in corresponding planar images.

Defining ROIs in SPECT images

Specific details of defining ROIs using SPECT images are presented as Supplementary Material. Briefly, using 3D image analysis software (3D slicer, version 4.3.1), SPECT images were volume-rendered to create a 3D reconstruction of the colon. Fiducial markers were placed at appropriate points along the colon to define ROIs. A second independent observer reviewed the positions of the fiducial markers and verified the ROIs drawn. All ROIs were drawn with the observer blinded to the patients’ clinical symptoms.

Planar images

The percentage activity in each ROI was calculated for each time point using computer software (Xeleris; GE Healthcare). This was achieved by determining the counts in each ROI as a proportion

of total ingested activity (total abdominal counts at first imaging [i.e. at 3 hours]). Corrections were made for isotope decay and background activity, as well as for tissue attenuation using the geometric mean of corresponding anterior and posterior scans^{37, 38}. At all other times points after 3 hours, the amount of radioactivity passed within stools (Region 8) was found indirectly by subtracting total decay- and attenuation-corrected abdominal counts at each time point from initial attenuation-corrected abdominal counts. **All analyses were performed blinded to the patients' clinical symptoms.**

In quantifying colonic transit, the following outcomes were measured from planar studies:

- (i) colonic geometric centre at each time point;
- (ii) percentage tracer retained at each time point. From this, the time taken for one-half of the tracer to be emptied from the colon ($T_{1/2}$) was calculated; and
- (iii) colonic geometric centre gradient or 'velocity'.

Colonic Geometric Centre

Overall colonic transit was summarised as the colonic geometric centre (GC) of isotope mass at each time point. As described in previous studies³⁹⁻⁴³, the GC was calculated as the weighted average of counts in the different ROIs, with the region number corresponding to its weighting factor. Thus, at any time, the proportion of counts in each colonic region was multiplied by its weighting factor as follows:

$$GC = ([\%pre-colon \times 0] + [\%AC-1 \times 1] + [\%AC-2 \times 2] + [\%TDC-1 \times 3] + [\%TDC-2 \times 4] + [\%TDC-3 \times 5] + [\%TDC-4 \times 6] + [\%NR \times 7] + [\% stool \times 8]) / 100$$

In this manner, the GC represented a region number between 0 and 8 where 50% of radioactivity lay on either side. A higher GC thus implied that the centre of the activity had progressed further toward the left side of the colon (or was even possibly eliminated in stool), whereas a lower GC suggested that the centre of the activity was still only in the proximal colon.

Percentage Tracer Retained

The overall percentage tracer retained within the entire colon was determined at each time point. With this information, a time-activity curve was generated for each patient. In recognising that these display a sigmoidal shape, a curve of best fit was generated for each patient which followed a 3rd-degree polynomial function (Microsoft Excel 2011; Microsoft Corporation, Redmond, Washington, U.S.A.). Accordingly, this equation was expressed as the following:

$$y = At^3 + Bt^2 + Ct + 100$$

where y = percentage tracer retained

t = time (in hours)

A , B , and C = polynomial coefficients

The intercept was set at 100, given that percentage tracer retained at time ‘zero’ was 100%, by definition.

Colonic Half-Clearance Time

From each polynomial equation generated, the colonic half-clearance time ($T_{1/2}$), defined as the time taken for one-half of the radioactive tracer to empty from the colon, was calculated for each patient (Microsoft Excel 2011; Microsoft Corporation).

Colonic Geometric Centre ‘Velocity’

Most previous studies have given only an index of the rate of transit based upon ‘static’ parameters such as the colonic GC at individual time points⁴⁴. Unfortunately, such measures do not provide a temporal index of transit disturbance. To help resolve this, one additional variable was defined: the ‘velocity’ of GC progression, reflected by the ‘gradient’ of the overall time-GC curve. To achieve this, a logarithmic curve of best fit was applied to individual time-GC curves (Microsoft Excel 2011; Microsoft Corporation), and an equation for the curves of each patient was generated in the format:

$$y' = A \log_e t$$

where y' = colonic GC

A = 'gradient' of the curve

t = time (in hours)

The intercept of the equation was suppressed at 'zero', because the GC at time '0' must be zero, by definition.

The 'gradient' of the curve generated, A , was interpreted as a measure of colonic GC 'velocity', and will be referred to as the 'GC velocity index' herein. To give a degree of validation to this new variable, it was compared with other measures of colonic transit, namely the position of the colonic GC at 32 and 48 hours.

SPECT Images

Similar to the processing of planar images, the percentage activity in each 3D-ROI established with SPECT was calculated for each time point using computer software (3D slicer, version 4.3.1). This was accomplished by determining the proportion of counts within each 3D-ROI as percentage of retained tracer at each time point; absolute values of tracer retention were determined using data from planar scintigraphy. The main parameter measured from the SPECT studies was the 'volumetric centre', which effectively summarises the median position of tracer distributed across 3D-ROIs based on volumetric counts. At any time, the proportion of counts in each colonic region determined by SPECT was multiplied by its weighting factor, as described above. Accordingly, as with the interpretation of GCs, the VC represented a region number between 0 and 8 where 50% of radioactivity lay on either side.

Statistical Analyses

Data were expressed as grouped results, with central tendencies presented as mean \pm standard deviation (SD) when data was normally distributed or as median (range) for non-parametric data. Frequency and percentages were expressed for categorical variables. Comparison of test groups (i.e. 'no LARS', 'minor LARS', and 'major LARS') was performed using the non-parametric Kruskal Wallis test (SPSS version 21, Chicago, IL, USA). If the Kruskal Wallis test was statistically significant or showed a trend ($P < 0.10$), *post-hoc* analyses were performed using the Mann-Whitney *U* test for pairwise comparisons of individual LARS groups. For all tests, $P < 0.05$ was considered to show a significant difference.

The ability of the colonic GC, percentage tracer retained, $T_{1/2}$, and 'GC velocity index', to differentiate 'major LARS' from 'no LARS', and separately 'minor LARS' from 'no LARS' was further analysed using logistic regression. A summary of the discriminant ability of these values was generated based on receiver operating characteristic curves (ROC) as well as the corresponding area under the ROC curves (AUC values). The models that yielded the largest AUC values were determined. Cut-off values were calculated by identifying the co-ordinates that minimised the Euclidean distance between the ROC curve and the upper left corner of the ROC graph (which represents the point of 100% sensitivity and specificity).

RESULTS

Patient Characteristics

Of the 50 study patients, 37 were male (mean age 72.3 years [SD 9.0]). The mean time since surgery was 6.2 years (SD 2.8). All patients completed the study, with no adverse events recorded.

Bowel symptoms

The bowel symptoms reported by the study patients as well as calculated LARS scores are presented in Table 1. The median LARS score for the study population was 21 (out of 42 [range 0-41]). Over one-third of patients ($n=17$, 34%) were classified as having ‘major LARS’, nine patients (18%) had ‘minor LARS’ while the remaining 24 patients (48%) had no evidence of LARS. Further stratification of results was according to these three subgroups. The clinico-pathological features of the study cohort are presented in Table 2. Overall, there were no differences in the clinico-pathological features of patients between subgroups of patients.

Planar and SPECT Scintigraphy

All patients completed the entire protocol with planar and SPECT images acquired at the specified time points. Examples of planar images obtained are presented in Figure 2A, and the corresponding SPECT images are presented in Figure 2B.

Fiducial markers were placed on SPECT/CT images, as shown in Figure 3. From this, volume-rendered SPECT images were divided into 3D-ROIs (Figure 4A). Using the 3D-ROIs as a guide, equivalent ROIs were drawn on the planar images (Figure 4B).

Colonic Geometric Centre

The colonic GC at each time point, stratified by LARS group and summarised for the entire study

cohort, is presented numerically in Table 3 and graphically in Figure 5. Notably, there were significant differences between the colonic GCs measured for the subgroups at 32 and 48 hours ($P=0.015$ and $P=0.026$, respectively). Furthermore, *post-hoc* analyses demonstrated that the significant differences in GCs were between the ‘no LARS’ and ‘major LARS’ subgroups at both 32 hours ($P=0.012$) and 48 hours ($P=0.025$), with the median GCs at both time points being almost two ROIs greater (i.e. two segments further along [more distal] in the colon) in patients with ‘major LARS’ compared to those with ‘no LARS’. At these same time points, however, the GCs between patients with ‘no LARS’ and ‘minor LARS’, and between those with ‘minor LARS’ and ‘major LARS’, were similar ($P>0.05$).

Colonic Tracer Retention

The percentage colonic tracer retention at each time point, stratified by LARS group and summarised for the entire study cohort, is presented numerically in Table 3 and graphically in Figure 6 as time-activity curves. There were significant differences noted in percentage tracer retained between the subgroups of patients at 24, 32, and 48 hours ($P=0.01$, $P=0.002$, and $P=0.012$, respectively) (see Figure 6B). Furthermore, similar to findings with colonic GCs, *post-hoc* analyses demonstrated that the significant differences in percentage retention between the LARS groups were specifically driven by differences between the ‘no LARS’ and ‘major LARS’ groups. At each of the time points, the percentage colonic retention was significantly lower in patients with ‘major LARS’ compared with those with ‘no LARS’ (6 hours: $P=0.034$; 24 hours: $P=0.007$; 32 hours: $P=0.001$; and 48 hours: $P=0.013$), indicating faster excretion and thus colonic transit. However, percentage colonic retention between patients with ‘no LARS’ and ‘minor LARS’, and ‘minor LARS’ compared with ‘major LARS’, were similar at these time points ($P>0.05$).

Colonic Half-Clearance Time

An example of a time-activity curve for an individual patient with the corresponding colonic half-

clearance time (i.e. $T_{1/2}$) is shown in the Supplementary Figure (A). In this example, the curve of best fit follows a 3rd-degree polynomial form, and the corresponding equation is shown ($R^2=0.994$). The $T_{1/2}$ for this curve is calculated to be 46.58 hours.

There were significant differences in colonic half-clearance times ($T_{1/2}$) between the subgroups. The median $T_{1/2}$ values of patients ‘no LARS’, ‘minor LARS’, and ‘major LARS’ were 57.0 hours (range 32.1–160.0), 45.4 hours (11.5–138.9), and 38.3 hours (17.0–65.0), respectively ($P=0.005$). Again, *post-hoc* analyses revealed that the significant differences were driven specifically by those between patients with ‘no LARS’ and ‘major LARS’ ($P=0.003$), indicative of accelerated transit in ‘major LARS’ patients. $T_{1/2}$ values were similar in the other subgroup comparisons.

Geometric Centre Velocity Index

An example of a time-GC curve for an individual patient, along with its associated logarithmic equation, is shown in the Supplementary Figure (B). Good logarithmic curve estimations were established for each time-GC curve (median r^2 0.87) in all patients. For the entire study cohort, the median GC velocity index calculated was 1.560. The GC velocity index was validated against the GCs at 32 and 48 hours. These time points were chosen because they were most able to discriminate the colonic transit profiles of the three LARS subgroups (see above). At both time points, the GC velocity index demonstrated strong linear correlation with the colonic GC: $r^2 = 0.875$ at 32 hours, and $r^2 = 0.888$ at 48 hours ($P<0.001$ for both).

Significant differences were observed between patients in each of the subgroups with median indices of patients with ‘no LARS’, ‘minor LARS’, and ‘major LARS’ being 1.45 (range 0.98–1.80), 1.62 (1.05–2.04), and 1.70 (1.18–1.92), respectively ($P=0.016$). *Post-hoc* analyses again revealed that the significance was driven specifically by difference between patients with ‘no LARS’ and ‘major LARS’ ($P=0.013$), with indices being similar between the remaining groups ($P>0.05$).

'Volumetric' Centre

Linear regression revealed a strong correlation between the volumetric and geometric centres measured by SPECT and planar studies, respectively. At 6 hours, the Pearson correlation between the two parameters was 0.946 ($r^2 = 0.895$), whilst the Pearson correlations at 24 and 32 hours were 0.984 ($r^2 = 0.969$) and 0.990 ($r^2 = 0.981$), respectively. There was a trend toward differences in the volumetric centres measured between the LARS groups at 24 and 32 hours, but these failed to reach statistical significance. Individual pairwise comparisons between the groups, however, demonstrated that there were significant differences between patients with 'no LARS' and 'major LARS' at 24 hours (median 3.60 [range 1.87–6.26] vs. 5.04 [1.63–7.25; $P=0.011$]) and 32 hours (4.27 [1.86–6.91] vs. 5.96 [2.13–7.51]; $P = 0.022$), again indicating faster colonic transit in the 'major LARS' group, similar to findings based on planar colonic GCs.

Receiver Operating Curve Characteristics

ROC curves were used to further assess the ability of the following end-points to differentiate patients with 'major LARS' from those with 'no LARS': (a) colonic GC at 32 and 48 hours; (b) percentage tracer retained at 24, 32, and 48 hours; (c) GC velocity index; (d) $T_{1/2}$; and (e) volumetric centre at 24 and 32 hours. The endpoints that yielded the largest AUC discriminatory values were: (i) percentage tracer retained at 32 hours (AUC 0.828); (ii) $T_{1/2}$ (AUC 0.804); (iii) GC velocity index (AUC 0.775); and (iv) colonic GC at 32 hours (AUC 0.772). The ROC curves for these analyses, as well as the associated AUC values, are presented in Figure 7. Cut-off values of each of these endpoints were then determined by calculating the co-ordinates on the ROC curve with the shortest Euclidean distance to the upper left corner. When considering percentage tracer retained at 32 hours, a cut-off value of 82.2% provided 82% sensitivity and 75% specificity in discriminating between patients with 'major LARS' and 'no LARS'. The cut-off values and corresponding sensitivities/specificities of the other parameters are as follows: (i) $T_{1/2}$: 47.04 hours (77% sensitivity, 75% specificity); (ii) GC

velocity index: 1.55 (77% sensitivity, 67% specificity); and (iii) colonic GC at 32 hours: 5.3 (71% sensitivity, 83% specificity).

Similar ROC curves were also generated to compare patients with ‘minor LARS’ and ‘no LARS’, but are not presented as they yielded poor AUC values (<0.650). These low AUC values were consistent with the observation that endpoints were not statistically different on initial non-parametric tests.

DISCUSSION

This prospective study is the first to objectively measure colonic transit following AR using scintigraphy (the gold standard) in a large number of patients, allowing comparison between subgroups of patients based on postoperative bowel function. To overcome the potential confounding issue of disrupted colorectal anatomy in postoperative patients, the novel use of SPECT/CT imaging provided more accurate and three-dimensional appreciation of anatomy. To summarise the key findings, this study demonstrated differences in colonic transit between patients with differing degrees of bowel dysfunction postoperatively. Specifically, patients with ‘major LARS’ had significantly faster colonic transit compared with patients with ‘no LARS’, as evidenced by higher GCs at 32 and 48 hours, lower retention of tracer at 24 and 32 hours, shorter colonic half-clearance times, and higher GC velocity indices.

Study Protocol

Anticipation that transit could be accelerated in a proportion of patients and considerations of altered colonic anatomy resulted in a study protocol that was modified substantially from that usually employed to investigate delayed/slow colonic transit. Specifically, the protocol required an increased frequency of scanning in the early period to ensure that patients with accelerated transit were adequately characterised, which is different from standard protocols where images are not usually obtained on day one²⁴. However, image acquisition continued for five days to ensure no patients with delayed transit (e.g. possibly secondary to evacuation dysfunction) were missed.

The novel use of SPECT to provide additional information regarding the 3D anatomy of the colon and rectum deserves further discussion. Traditionally, the use of SPECT has been confined to imaging structures such as the brain²⁷, heart²⁸, and lungs²⁹, and has found utility in these circumstances owing to the superior 3D spatial resolution that it confers over planar imaging. More recently, studies have

probed whether similar advantages of SPECT could be drawn to imaging pathologies of the gastrointestinal tract^{30, 45}. This consideration is particularly relevant when evaluating patients following AR, seeing as complete mobilisation of the left colon and splenic flexure and resection of the recto-sigmoid necessarily results in alteration of colonic anatomy. To also address this, the colon was divided into ROIs based on length. This approach, however, requires an accurate appreciation of colonic length in three-dimensions, a requirement that was well served by SPECT.

Transit Parameters

Numerous transit parameters were measured/calculated in this study including: (i) geometric centre (GC); (ii) percentage tracer retention; (iii) colonic half-clearance time ($T_{1/2}$); (iv) GC velocity index; and (v) volumetric centre. The colonic GC and percentage tracer retention have both been used as endpoints in previous transit studies⁴⁶. Further, the majority of these studies have relied on these two parameters as indices for the *rate* of transit. It should be noted, however, that the colonic GC and percentage tracer retention are ‘static’ measurements at *individual* time points and, in themselves, do not completely summarise the spatial progression of isotope over time. In an attempt to resolve this, time-activity analyses for the colonic GC and percentage tracer retained were employed, from which two additional parameters (GC velocity index and $T_{1/2}$, respectively) were calculated.

Calculation of a velocity index to summarise a time-GC curve was first described in this journal by Scott *et al.* (2001), who defined the gradient of GC progression as reflecting velocity of isotope transit in patients being investigated for slow transit constipation²⁴. In that study, spatial progression of isotope was quantified for the entire study period by ‘linearising’ the time-GC curves for each patient and calculating the slope of the line of best fit. Such an approach is attractive in principle, but such attempts in the present study would be erroneous due to the non-linear relationship demonstrated between time and GC in this study population. With this in mind, a more sophisticated approach was adopted to summarise the relationship between time and GC for each patient by creating a logarithmic

curve of best fit. This approach is justified by the high r^2 values obtained with these curves (median $r^2 = 0.87$). Each curve generated a natural logarithmic equation to summarise isotope transit; the coefficient of this equation was interpreted to be the ‘gradient’ of the time-GC curve, also referred to as the ‘GC velocity index’ in this study.

The colonic half-clearance time ($T_{1/2}$) is a parameter that has been used by previous studies^{47, 48} to reflect rate of transit, and measures the time taken for half of the ingested tracer to be evacuated. In the present study, time-activity curves of tracer retained were sigmoidal in shape, meaning that *linear* interpolation of points to calculate $T_{1/2}$ could potentially lead to inaccuracy. In preference to this, this study generated a polynomial function to summarise the time-activity curves of each patient, from which the $T_{1/2}$ could be accurately calculated by solving for the roots of each equation.

‘Volumetric centre’, which describes the weighted average distribution of tracer based on *volume*, calculated from SPECT images was uniquely calculated in the present study. This calculation may be seen as the ‘three-dimensional extension’ of the ‘geometric centre’ that is calculated from planar images. This new parameter could provide novel information to describe the mean position of isotope, based on the premise that SPECT provides superior 3D-spatial resolution to permit more accurate delineation of ROIs. However, it has yet to be formally validated as a true marker of transit, and is only able to be calculated at the limited time points that SPECT images are acquired.

Distinguishing ‘Major LARS’ from ‘Minor LARS’

Patients were stratified based on clinical symptoms of dysfunction into those with major, minor and no LARS, given that this is widely recognised as the most objective measurement of documenting symptoms severity following anterior resection. All patients included in the study underwent (at least partial) mobilisation of the rectum and had an anastomosis fashioned within 15 cm of the anal verge. Although this resulted in a somewhat heterogeneous study population, it was interesting to note that

even patients who underwent high anterior resection are at risk of LARS; indeed, one-third of these experienced major LARS. This study has shown that patients with ‘major LARS’ had significantly accelerated transit compared with patients with ‘no LARS’. Accordingly, measurement of transit using colonic scintigraphy is able to accurately discriminate between these subgroups of patients, although its ability to discriminate ‘minor LARS’ patients was less accurate. Specifically, patients with ‘major LARS’ had significantly; (i) higher GCs at 32 and 48 hours; (ii) lower percentage tracer retained at 6, 24, 32, and 48 hours; (iii) shorter $T_{1/2}$; and (iv) greater GC velocity indices compared with patients with ‘no LARS’. Furthermore, ROC curve analyses revealed that the endpoints most accurate in the differentiation of patients with ‘major LARS’ from ‘no LARS’ (based on AUC values) were: (i) percentage tracer retained at 32 hours (AUC 0.828); (ii) $T_{1/2}$ (AUC 0.804); (iii) GC velocity index (AUC 0.775); and (iv) colonic GC at 32 hours (AUC 0.772).

These findings objectively demonstrate physiological differences in the colonic transit of patients following AR that may help explain the clinical symptoms of bowel dysfunction following surgery. It is not surprising that patients with ‘major LARS’ (who experience more severe symptoms of storage dysfunction such as frequency and urgency), demonstrated concordant physiological derangements of accelerated colonic transit. By contrast, patients with ‘minor LARS’ and ‘no LARS’, who by definition experience less severe symptoms, displayed similar colonic transit. Further, it would appear from review of the time-activity and time-GC curves that images acquired at 32 hours are most informative in discriminating the transit profiles of the three subgroups of patients according to their LARS. The percentage tracer retained at 32 hours had the greatest AUC value in discriminating ‘major LARS’ from ‘no LARS’ patients. This suggests that scintigraphy findings at 32 hours may be useful to provide a physiological basis to support the symptoms described by patients with ‘major LARS’, and may be helpful in tailoring medical treatment (e.g. use of loperamide) to specific subgroups of patients with LARS but this would require confirmation in the setting of a comparative interventional study. These findings are also informative when considering protocol

refinement for future studies; while transit studies lasting for five days are arduous, timing of image acquisition may be potentially refined to 24, 32, and 48 hours if bowel dysfunction following AR is being specifically assessed.

Limitations

The prospective nature, large sample size of 50 patients and 100% completion of the study protocol by all subjects provided the strengths of this study. However, it was limited by the lack of ‘normative’ data obtained from healthy volunteers due to the inherent risks of exposure to ionising radiation. Accordingly, patients with an absence of clinical symptoms of dysfunction i.e. ‘no LARS’, were used to act as comparative group for those with ‘major LARS’ and ‘minor LARS’. Additionally, as with the introduction of any ‘new’ protocol, there is a requirement for prospective validation of the protocol. Prospective studies will help contribute to a dataset which specifically analyses the role of SPECT in transit scintigraphy. Finally, the ‘new’ parameters measured in this study (i.e. GC ‘velocity index’ and volumetric centre) also require validation in future studies.

CONCLUSION

This prospective study was able to objectively measure colonic transit in a large number of patients following AR using scintigraphy (the gold standard) with enhancement using SPECT, and demonstrated significant differences between subgroups of patients based on postoperative bowel function. Specifically, colonic transit was significantly accelerated in patients with ‘major LARS’ compared to those with ‘no LARS’, with the percentage tracer retained at 32 hours having the greatest AUC value in discriminating patients. Based on these initial observations, further comparative studies evaluating specific therapeutic interventions based on underlying colonic pathophysiology are warranted.

FIGURE LEGENDS

- Figure 1.** Schematic diagram of the colon following anterior resection, showing the ROI program used in this study. Due to the post-surgical anatomy of the patients, nine ROIs were defined: region 0 was proximal to the colon and region 8 represented faeces; the remaining 7 (regions 1-7) were within the colo-(neo)rectum, as shown.
- Figure 2. A. An example of serial planar images obtained (anterior and posterior images fused); B. Corresponding SPECT images (anterior, superior, and left views) obtained at 6, 24, and 32 hours. A – anterior, P – posterior, S – superior, I – inferior, R – right, L – left.
- Figure 3. Fiducial markers placed on fused SPECT images defined the boundaries of ROIs. A. Sagittal section – *7 marks pelvic inlet (dotted line connects sacral promontory to pubic symphysis); B. Axial section – *3 marks hepatic flexure; C. Coronal section – *1 marks caecal pole, *2 marks point midway between caecal pole (*1) and hepatic flexure (*3); D. 3D volume-rendered image – remaining fiducial markers (*4 – 6) placed by dividing colonic length between hepatic flexure (*3) and pelvic inlet (*7) into four equidistant segments.
- Figure 4. A. SPECT images (as displayed in Figure 2B), divided into seven ROIs based on fiducial markers placed. Cream – AC1; light blue – AC2, orange – TDC1, olive – TDC2, green – TDC3, purple – TDC4, yellow – neorectum; B. Planar images, as shown in Figure 2A, divided into ROIs as guided by corresponding SPECT images.
- Figure 5. A. Time-GC curve showing colonic GC versus time for the entire study cohort. Closed circles and error bars represent median values and interquartile range, respectively, at

each time point. Red line shows logarithmic line of best fit. B. Time-GC curves stratified according to LARS classification. Bullets represent median values for each LARS group. Dotted lines show corresponding lines of best fit.

Figure 6. A. Time-activity curve showing percentage tracer retained in the colon versus time for the entire study cohort. Closed circles and error bars represent median values and interquartile range, respectively. Dotted red line shows sigmoidal line of best fit. B. Time-activity curve stratified according to LARS classification. Bullets represent median values for each LARS group. Dotted lines show corresponding lines of best fit.

Figure 7. ROC curves showing discrimination between ‘major LARS’ and ‘no LARS’ groups based on: (A) percentage tracer retained at 24, 32, and 48 hours; (B) $T_{1/2}$; (C) GC velocity index; and (D) colonic GC at 32 and 48 hours.

Supplementary Figure.

A. An example of a time-activity curve for an individual patient. The curve of best fit is shown in red, along with its polynomial equation. The $T_{1/2}$ is shown graphically. B. An example of a time-GC curve for an individual patient. The curve of best fit is shown in red, along with its logarithmic equation.

Table 1. Bowel symptoms and LARS scores of study patients.

Outcome measure	Number (<i>n</i> = 50)	Per cent
Objective Symptoms		
Poor stool / flatus discrimination	38	76.0
Sensation of incomplete emptying	36	72.0
Incontinence to flatus	34	68.0
Toilet revisiting	33	66.0
Excessive straining	31	62.0
Faecal urgency	25	50.0
Bowel frequency (≥ 3 per day)	22	44.0
Unsuccessful evacuation	22	44.0
Sensation of anorectal obstruction	17	34.0
Incontinence to liquid stool	15	30.0
Hard stool	14	28.0
Incontinence to solid stool	11	22.0
Need for constipating medications	11	22.0
Need to self-digitate	8	16.0
Use of pads / plugs for faecal soiling	8	16.0
Evacuation time >10 minutes	4	8.0
Loose stools	2	4.0
Use of enema / suppository	0	0.0
LARS Score		
0 – 20 (No LARS)	24	48.0
21 – 29 (Minor LARS)	9	18.0
30 – 42 (Major LARS)	17	34.0

Table 2. Clinico-pathological features of study cohort

	No LARS (n = 24)	Minor LARS (n = 9)	Major LARS (n = 17)	OVERALL (n = 50)
	<i>n (%)</i> , mean ± SD			
Male (n, %)	18 (75%)	7 (78%)	12 (71%)	37 (74%)
Age (years)	72.7 (8.5)	76.0 (8.6)	70.0 (9.0)	72.3 (9.0)
Time since surgery (years)	6.8 (2.9)	5.1 (2.5)	5.9 (2.9)	6.2 (2.8)
ASA				
I	4 (17%)	2 (22%)	3 (18%)	9 (18%)
II	19 (79%)	5 (56%)	13 (77%)	37 (74%)
III-V	1 (4.2%)	2 (22%)	1 (6%)	4 (8%)
Neoadjuvant radiotherapy	1 (4%)	1 (11%)	2 (12%)	4 (8%)
Laparoscopic surgery	7 (29%)	6 (67%)	5 (29%)	18 (32%)
Tumour position				
Sigmoid (>15cm [#])	12 (50%)	5 (56%)	9 (53%)	26 (52%)
High rectum (11-15cm [#])	5 (21%)	1 (11%)	2 (12%)	8 (16%)
Mid rectum (6-10cm [#])	6 (25%)	3 (33%)	3 (18%)	12 (24%)
Low rectum (1-5cm [#])	1 (4%)	0 (0%)	3 (18%)	4 (8%)
Anastomotic height				
HAR (11-15cm [^])	13 (54%)	5 (56%)	9 (53%)	27 (54%)
LAR (6-10cm [^])	6 (25%)	1 (11%)	3 (18%)	10 (20%)
ULAR (1-5cm [^])	5 (21%)	3 (33%)	5 (29%)	13 (26%)
Tumour stage				
T-positive	18 (75%)	5 (56%)	13 (77%)	36 (72%)
N-positive	6 (25%)	4 (44%)	4 (24%)	14 (28%)
Apical lymph node harvested	16 (67%)	7 (78%)	13 (77%)	36 (72%)
Defunctioning ileostomy	11 (46%)	5 (56%)	9 (53%)	25 (50%)
Adjuvant chemotherapy	7 (29%)	4 (44%)	8 (47%)	19 (38%)
Use of constipating medications	1 (4%)	2 (22%)	8 (47%)	11 (22%)

[#]distance of lower tumour edge from anal verge; [^]distance of anastomosis from anal verge; ASA – American Society of Anaesthesiologists Score⁴⁹; HAR – high anterior resection; LAR – low anterior resection; ULAR – ultralow anterior resection

Table 3. Colonic geometric centre and percentage tracer retained at each time point, stratified by LARS group and summarised for entire cohort.

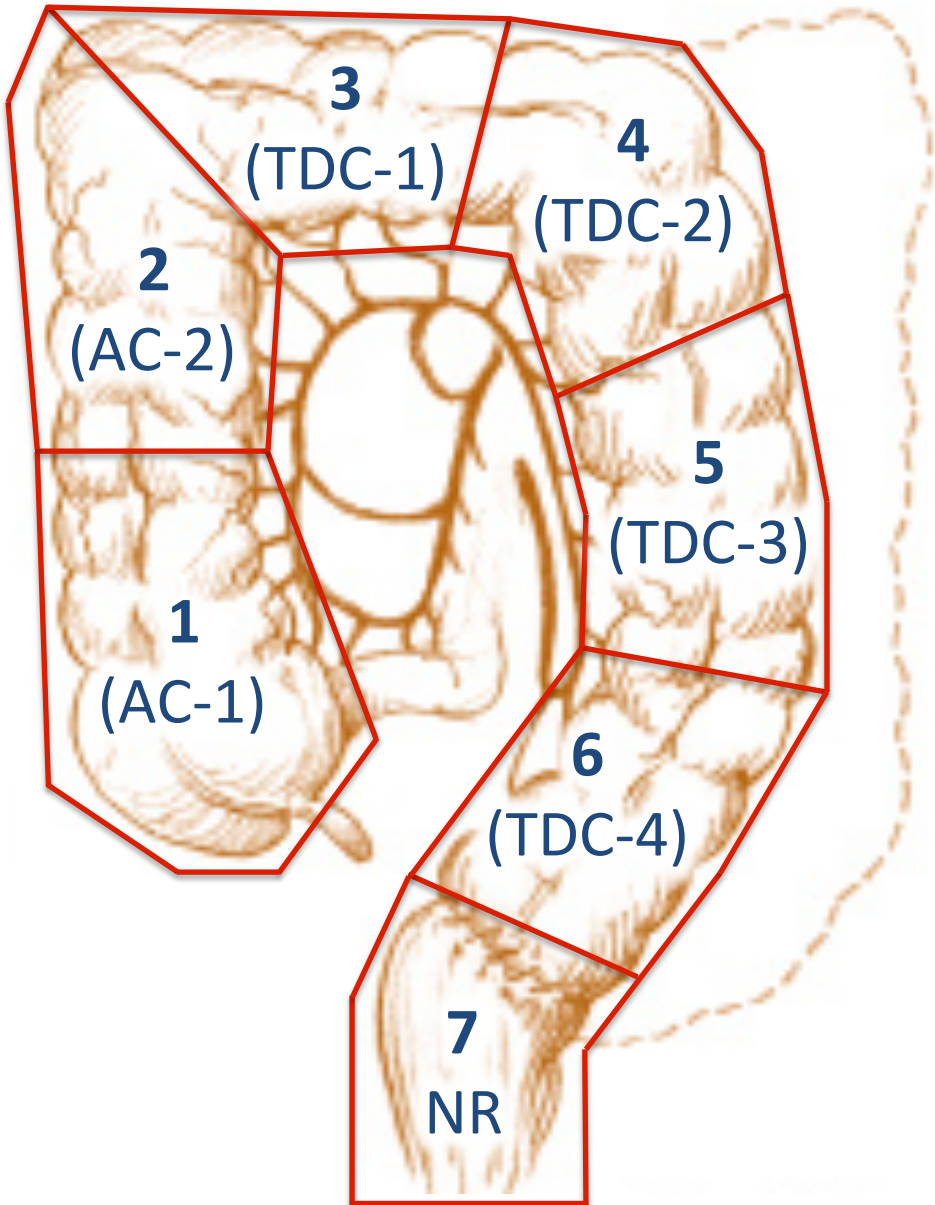
Transit parameter	No LARS (n = 24)	Minor LARS (n = 9)	Major LARS (n = 17)	P value	OVERALL (n = 50)
Colonic GC (median, range)					
3 hours	0.24 (0.00 – 2.82)	0.86 (0.16 – 3.38)	1.03 (0.00 – 3.41)	0.057	0.80 (0.00 – 3.41)
6 hours	1.26 (0.00 – 3.43)	2.43 (0.35 – 5.18)	1.53 (0.37 – 5.04)	0.182	1.52 (0.00 – 5.18)
24 hours	3.66 (2.23 – 5.75)	4.21 (1.78 – 7.69)	4.73 (1.79 – 6.98)	0.055	4.01 (1.78 – 7.69)
32 hours	4.30 (2.12 – 6.47)	5.16 (1.98 – 7.79)	5.94 (2.35 – 7.72)	0.015	4.61 (1.98 – 7.79)
48 hours	5.55 (2.64 – 7.96)	6.60 (4.17 – 7.97)	6.88 (3.97 – 7.90)	0.026	6.40 (2.64 – 7.97)
72 hours	7.54 (5.12 – 8.00)	7.57 (5.43 – 8.00)	7.67 (6.83 – 7.91)	0.328	7.58 (5.12 – 8.00)
96 hours	7.74 (5.94 – 8.00)	7.96 (6.29 – 8.00)	7.87 (7.34 – 8.00)	0.318	7.84 (5.94 – 8.00)
Percentage tracer retained (%, SEM)					
3 hours	100.0 (0)	100.0 (0)	100.0 (0)	1.000	100.0 (0)
6 hours	100.0 (0)	100.0 (5.3)	100.0 (1.0)	0.203	100.0 (1.0)
24 hours	95.1 (2.5)	88.9 (9.5)	82.3 (6.1)	0.010	90.2 (3.1)
32 hours	89.9 (3.4)	82.7 (10.1)	53.7 (6.5)	0.002	84.5 (3.7)
48 hours	75.1 (6.2)	54.0 (11.9)	29.8 (6.9)	0.012	52.8 (4.7)
72 hours	14.0 (6.5)	15.4 (9.6)	6.5 (3.1)	0.362	13.7 (3.9)
96 hours	7.6 (4.5)	1.0 (7.4)	3.5 (1.3)	0.297	4.5 (2.6)

GC – geometric centre; SEM – standard error of mean

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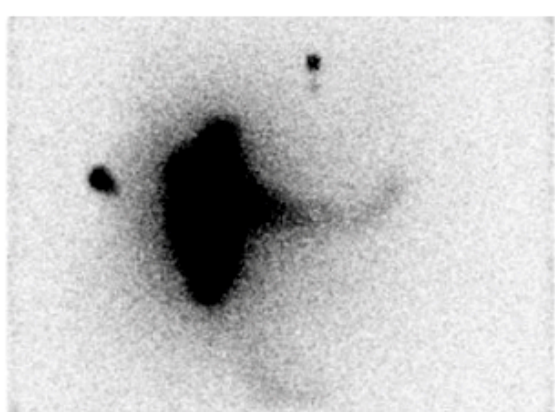
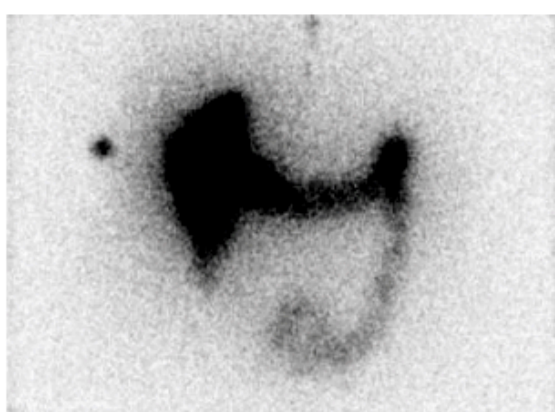
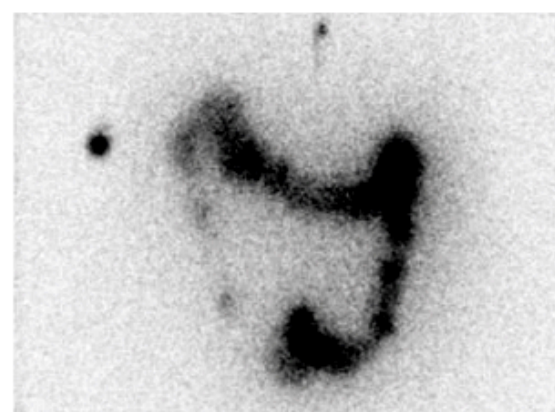
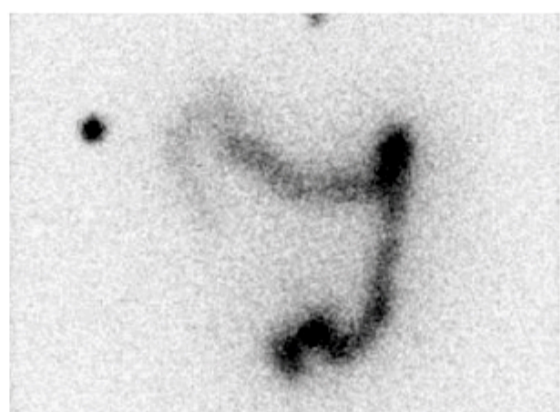
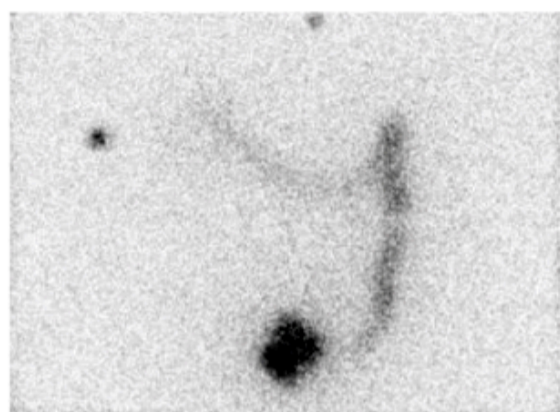
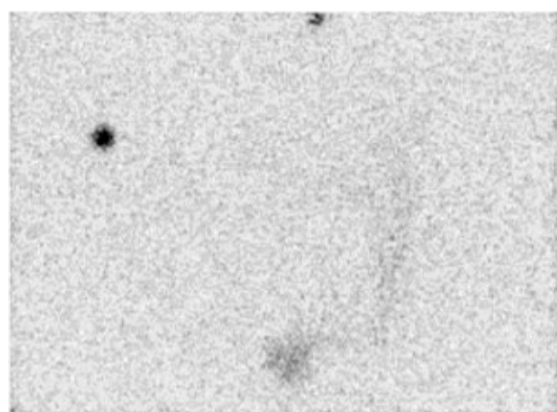
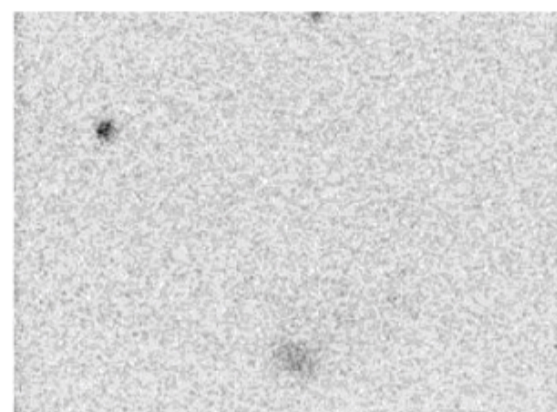
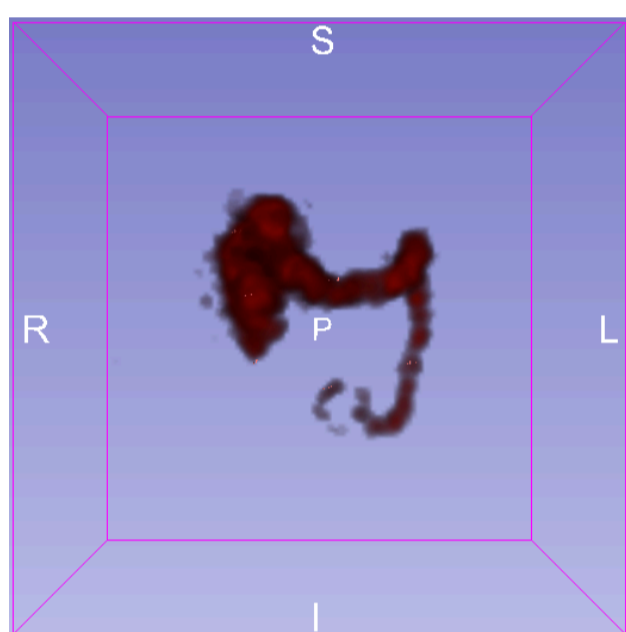
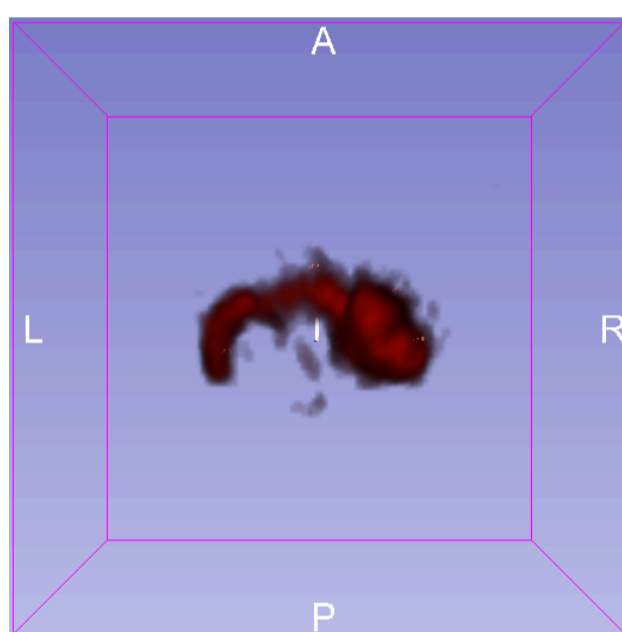
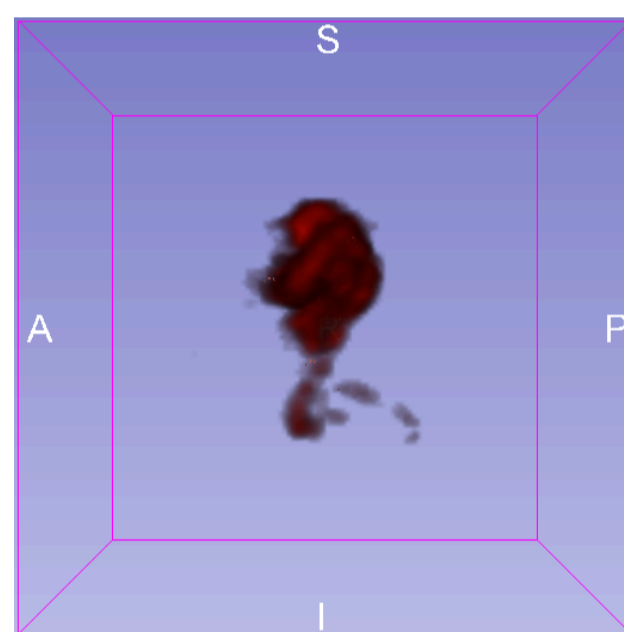
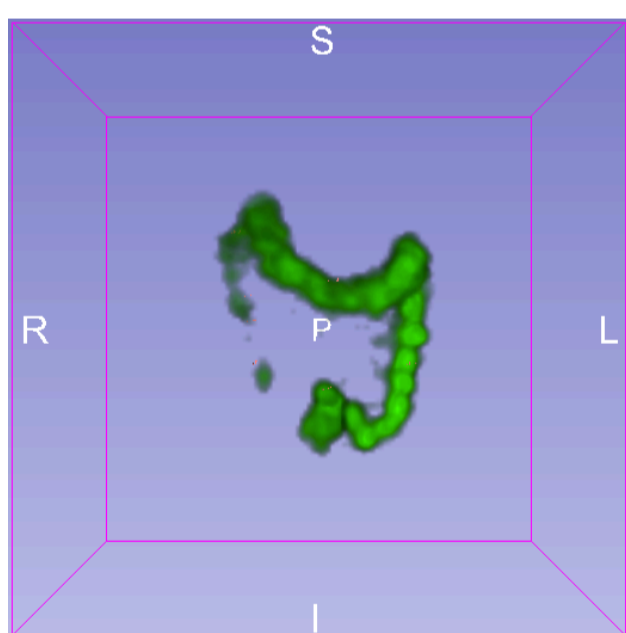
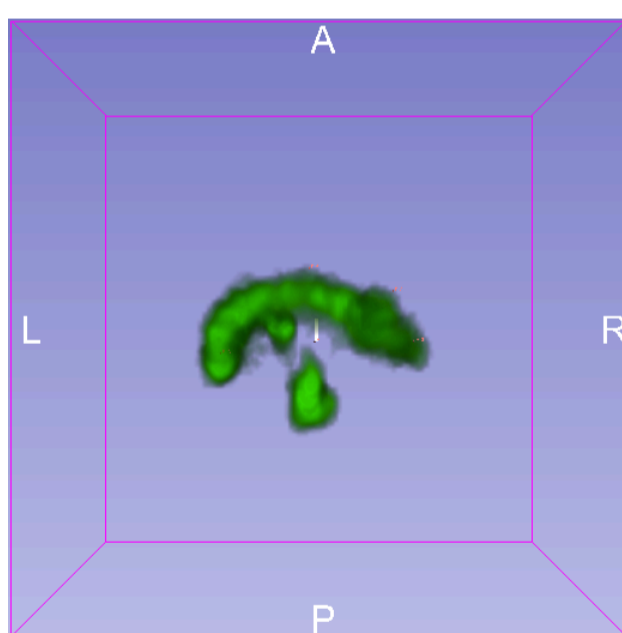
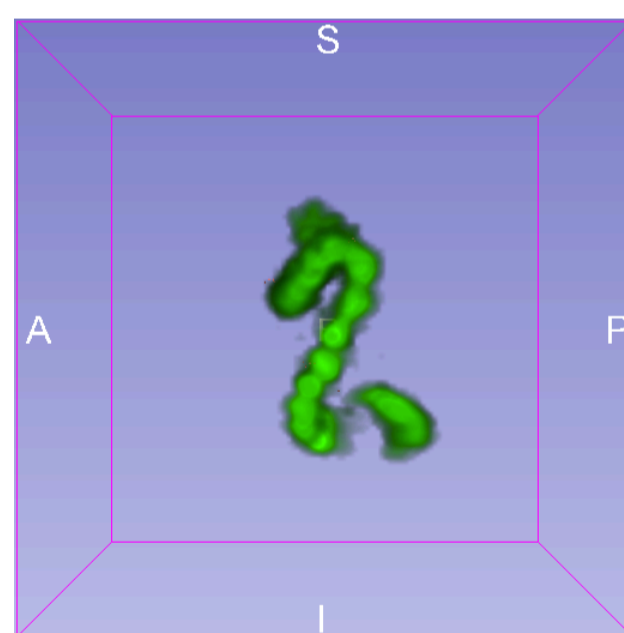
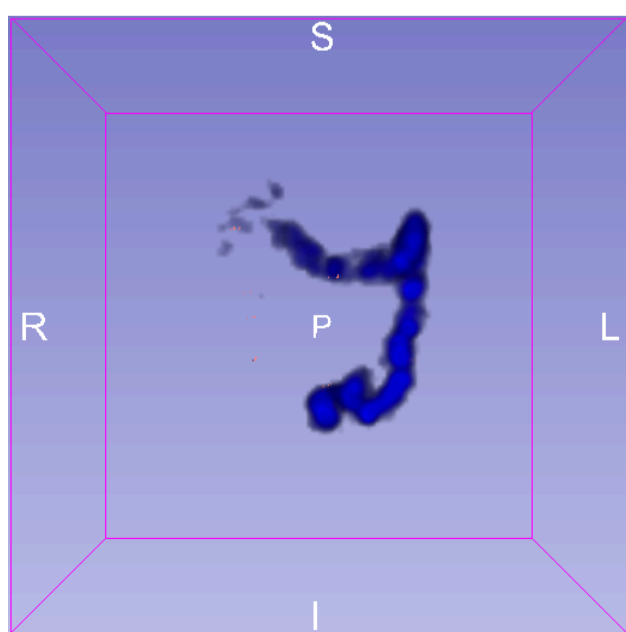
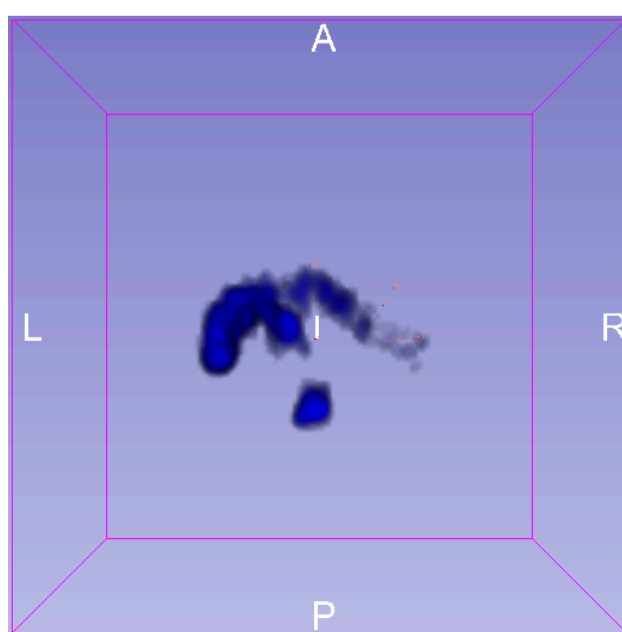
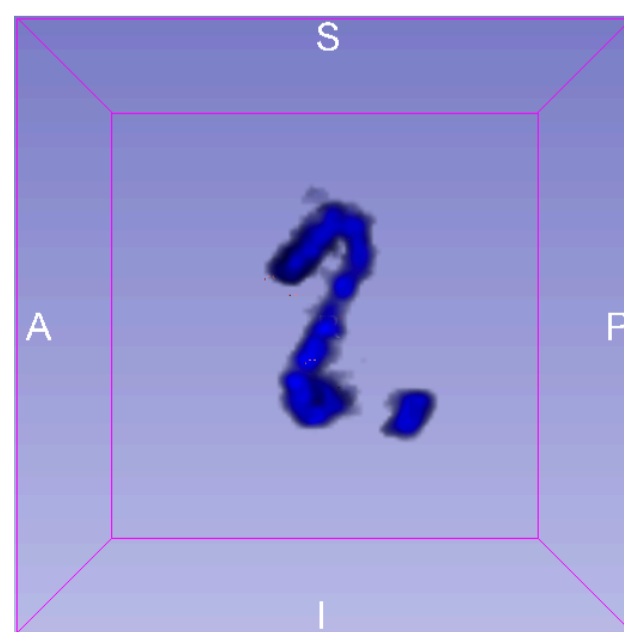
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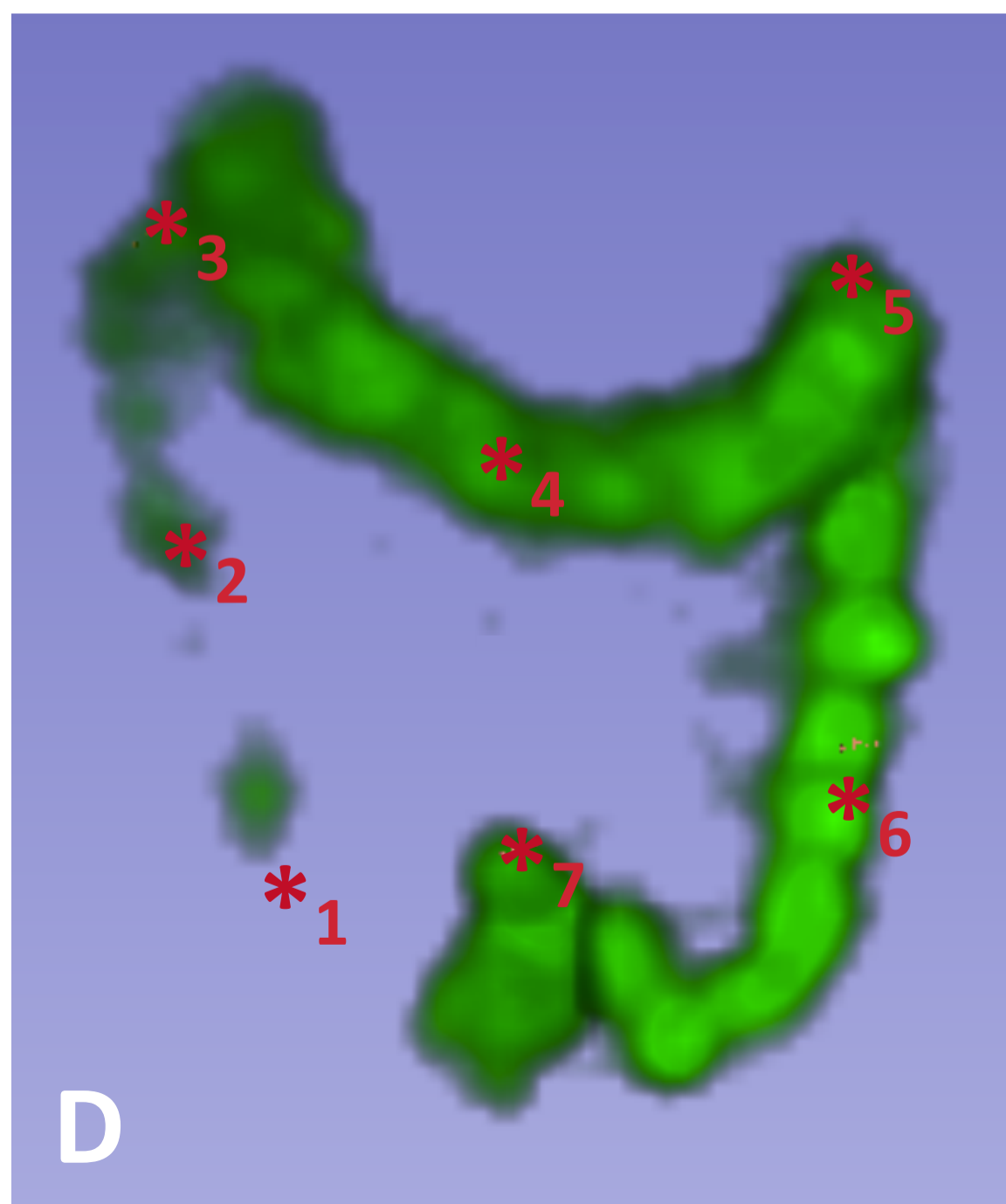
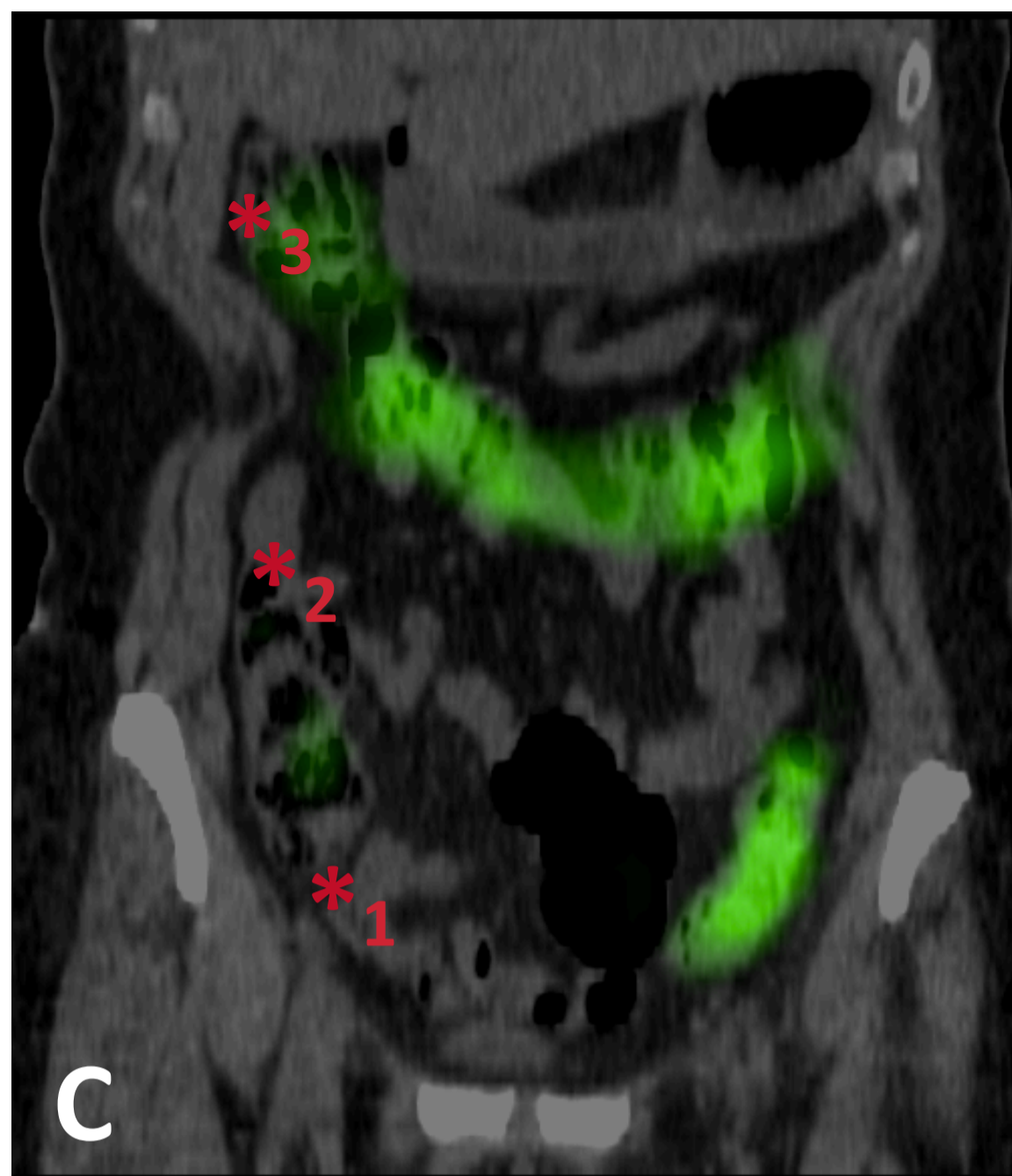
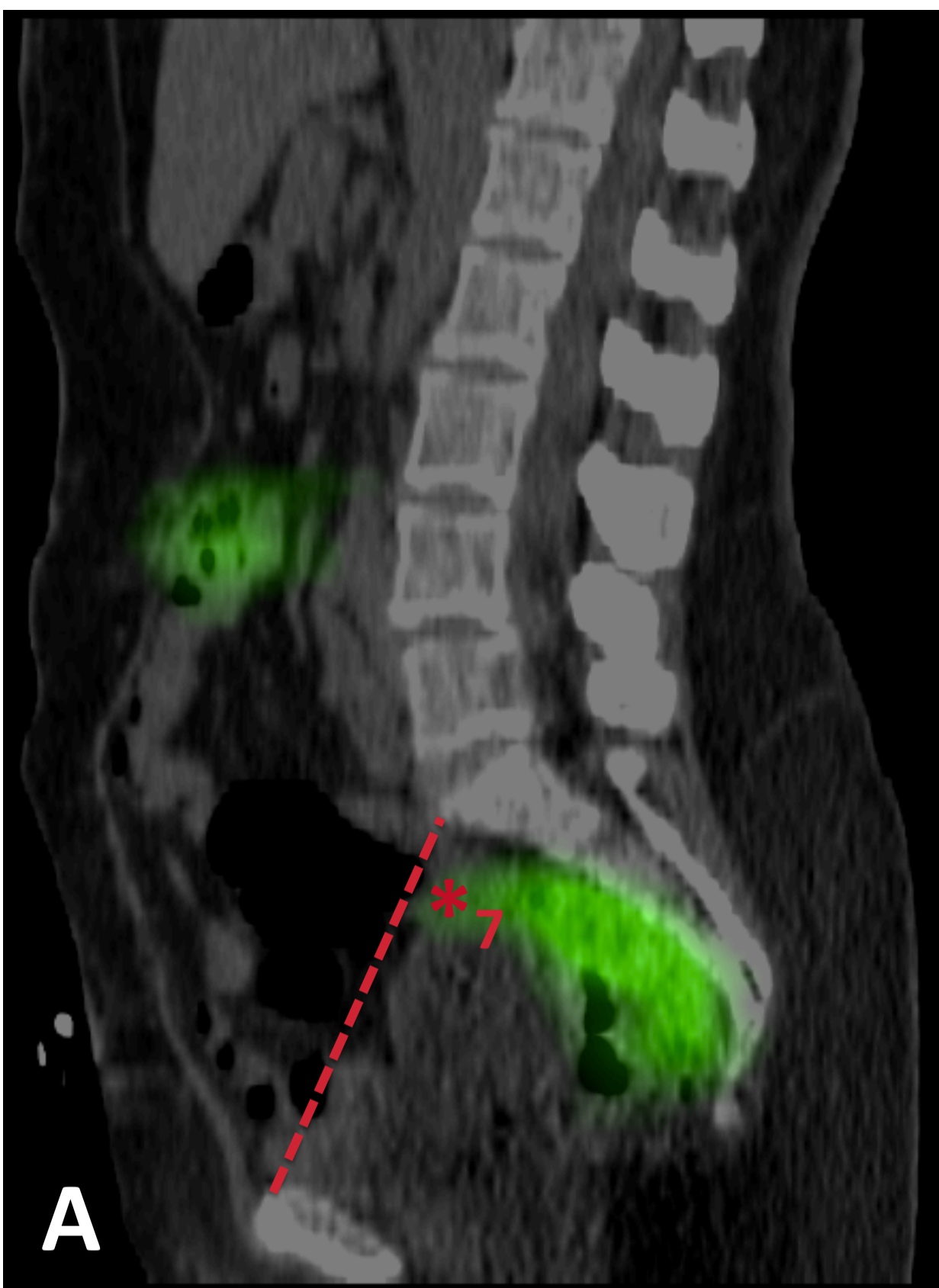
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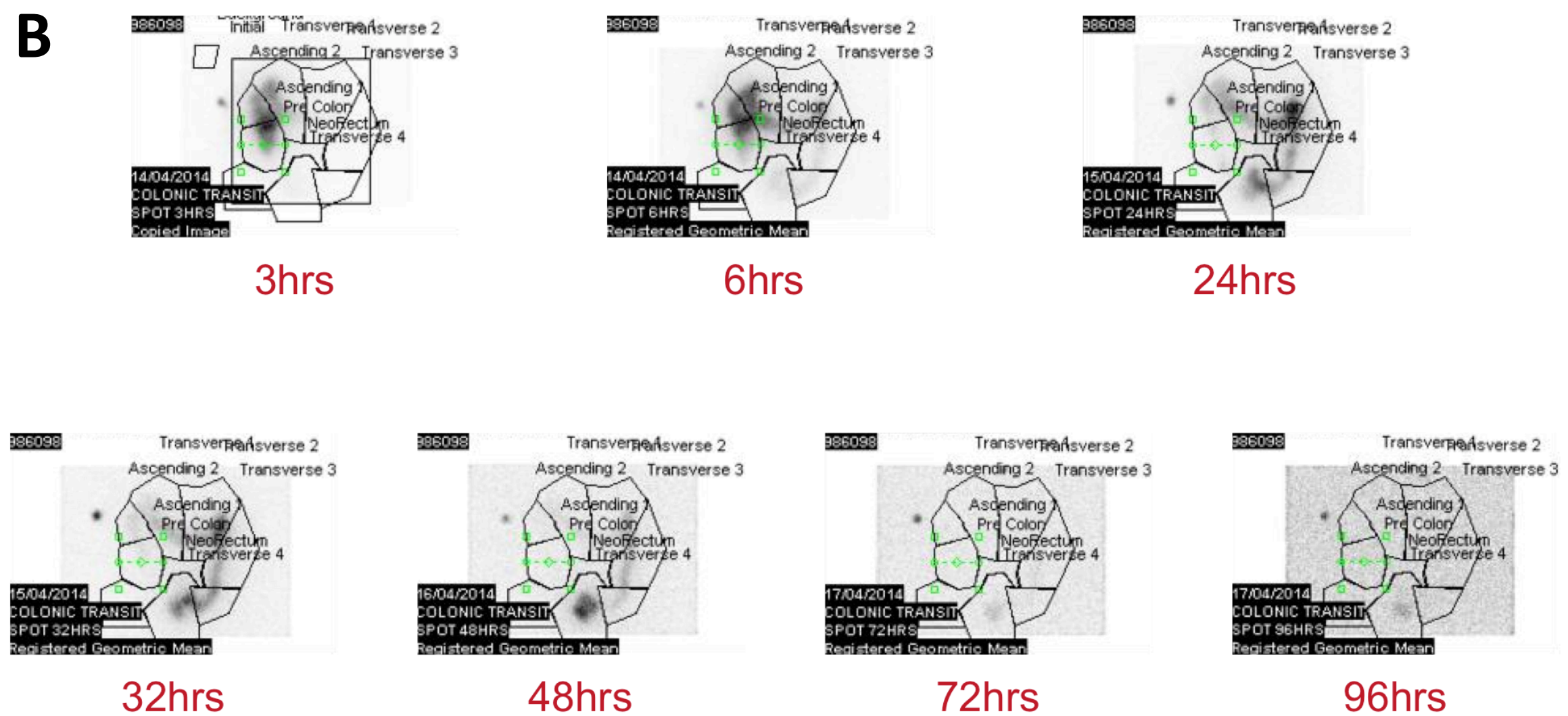
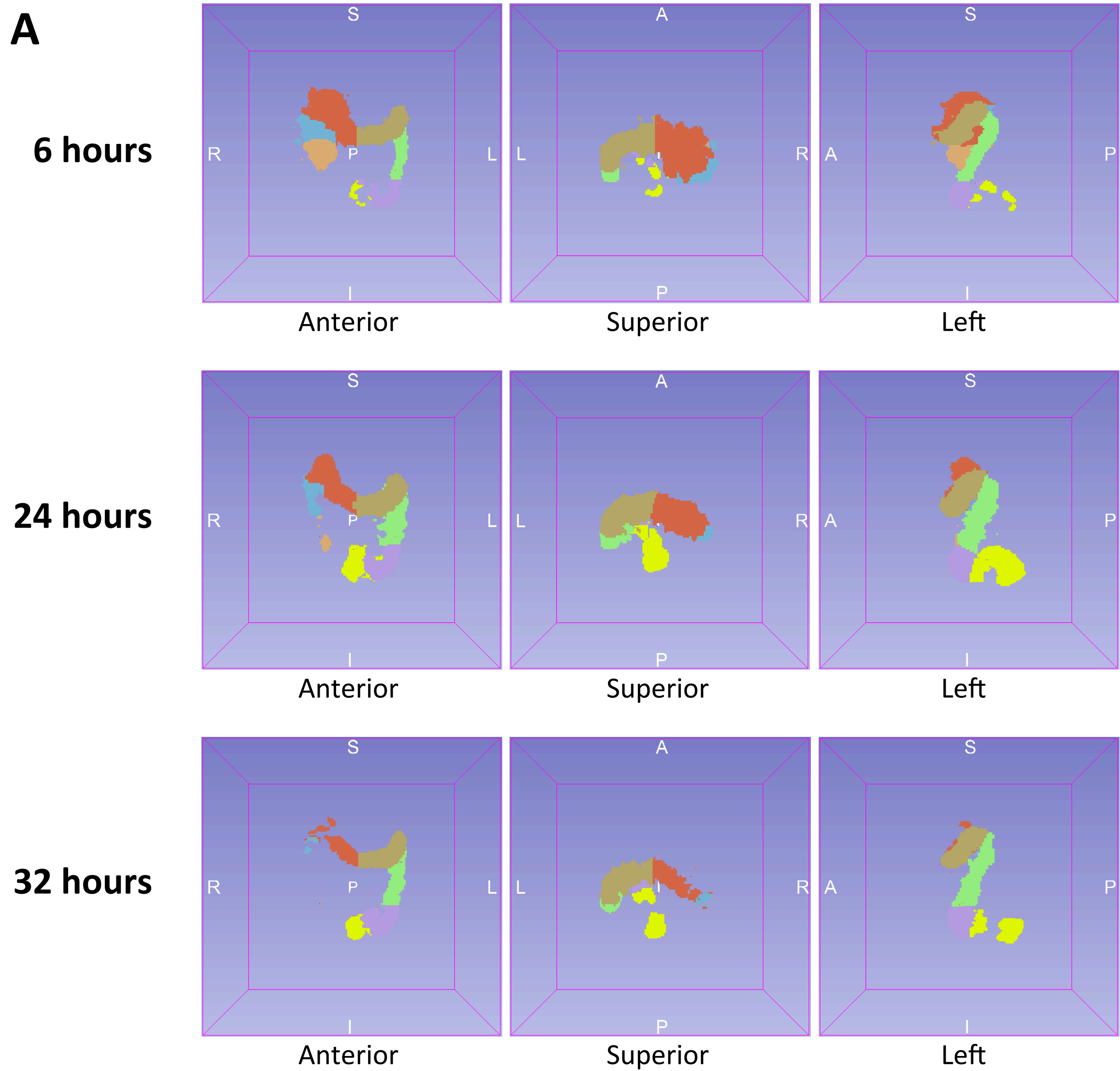
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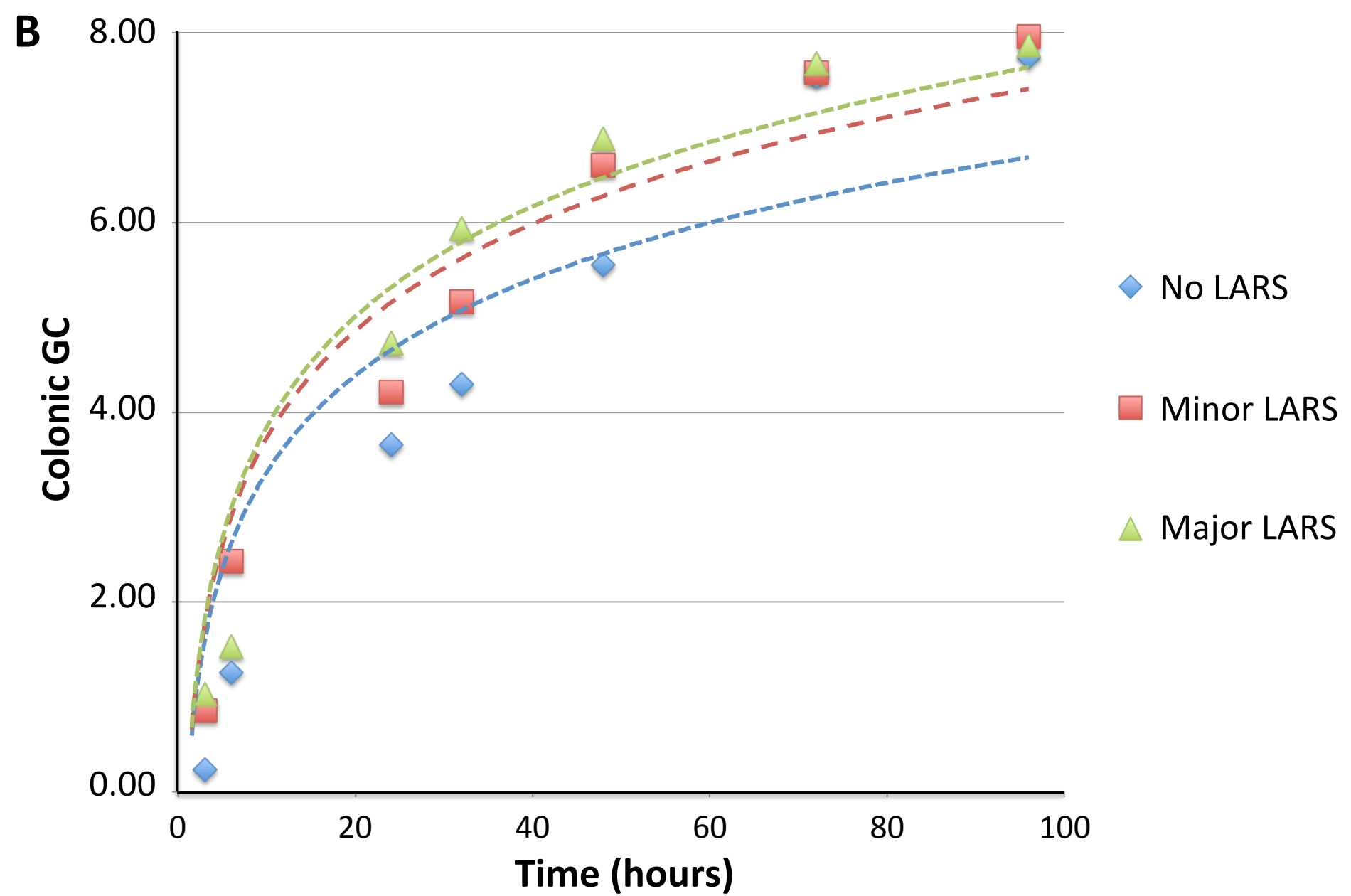
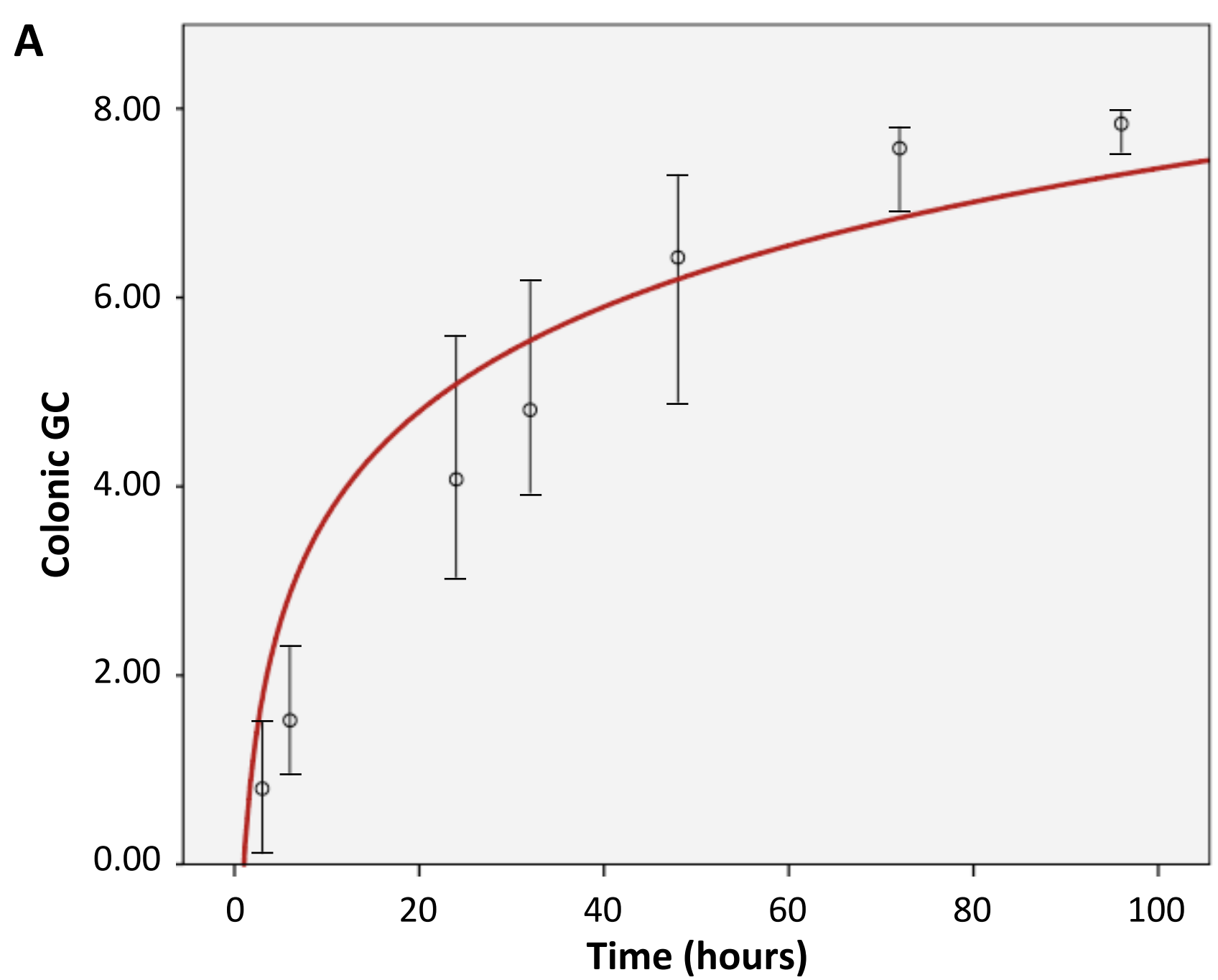
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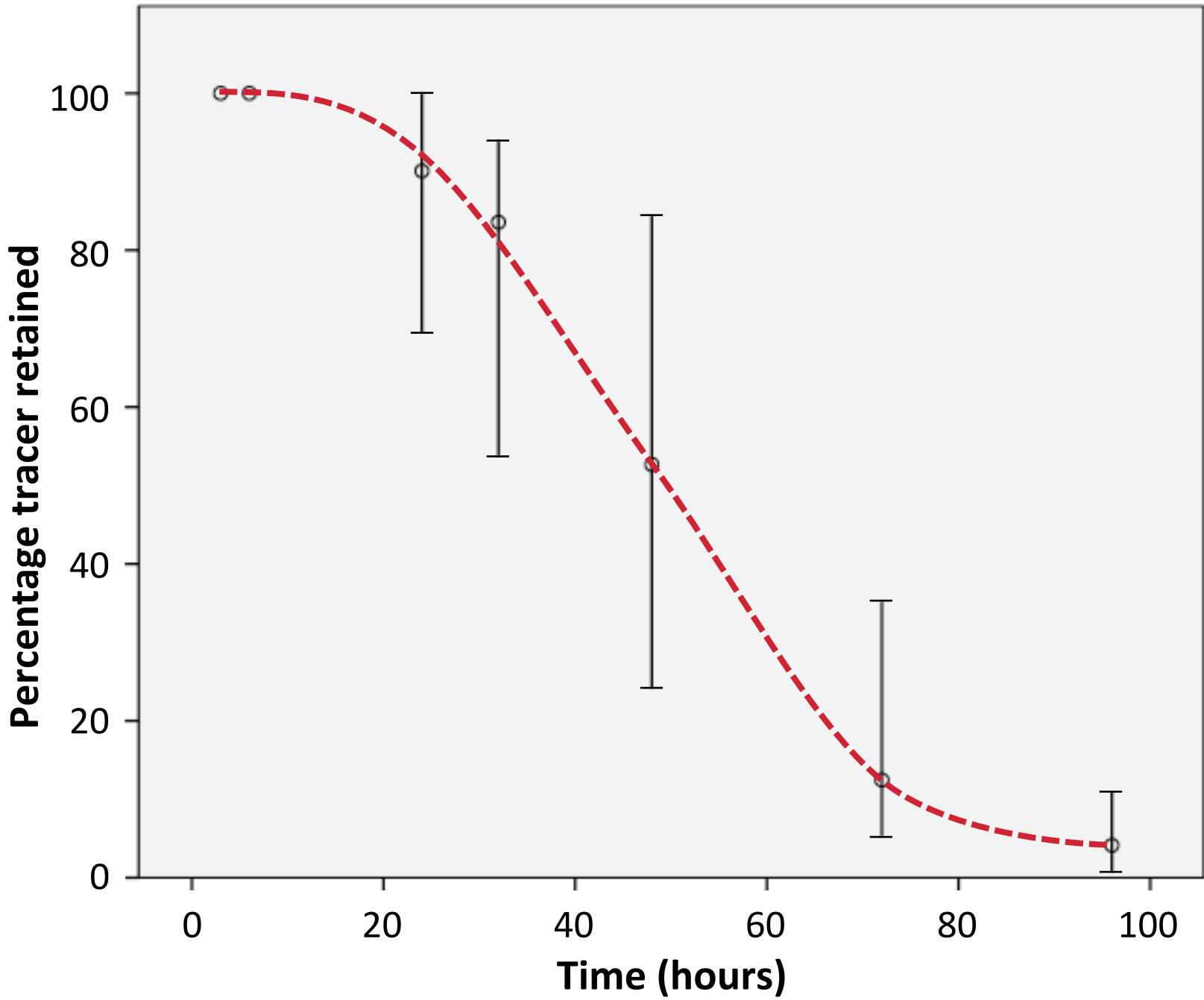
NR

A**3hrs****6hrs****24hrs****32hrs****48hrs****72hrs****96hrs****B****6 hours****Anterior****Superior****Left****24 hours****Anterior****Superior****Left****32 hours****Anterior****Superior****Left**







A**B**