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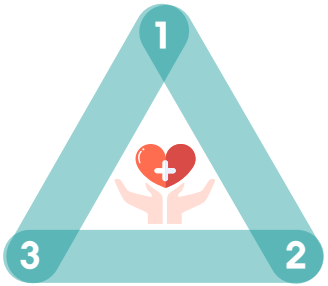

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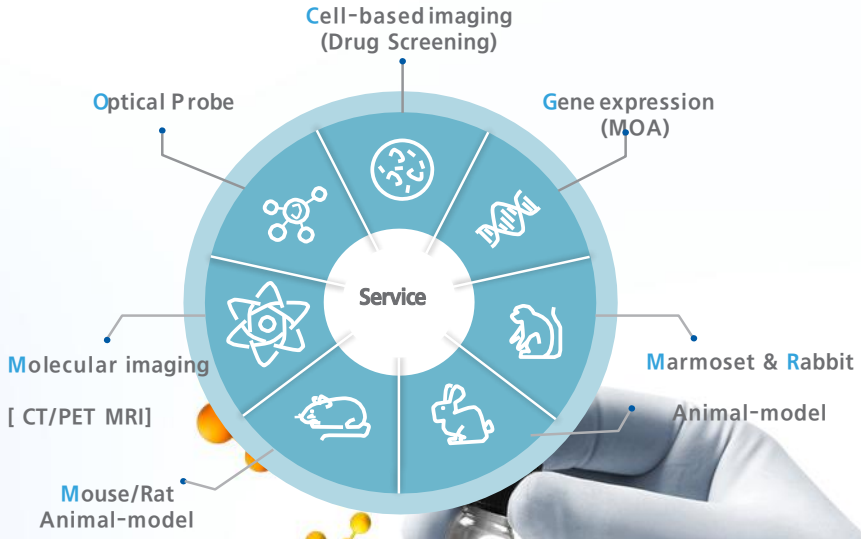

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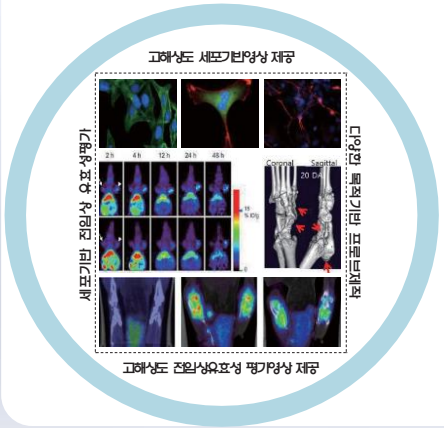


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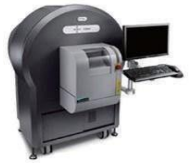
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Feasibility Assessment of Physical Factors of Rectal Cancer Short-Course Chemoradiotherapy with Delayed Surgery

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To verify the correlations between the clinical outcomes and physical factors of short-course chemoradiotherapy (SCRT) and long-course chemoradiotherapy (LCRT) with delayed surgery in patients with rectal cancer. Seventy-two patients with rectal cancer were enrolled in this study. Nineteen patients were treated with SCRT (25 Gy, 5 fractions) by intensity-modulated radiation therapy (IMRT), and 53 patients were treated with LCRT (50.4 Gy, 28 fractions) by three-dimensional conformal radiation therapy (3DCRT). Various physical factors for the target and organs at risk (OARs) were calculated to compare the clinical outcomes. The organ equivalent dose (OED) and lifetime attributable risk (LAR) of bowels and bladders were similar between the SCRT and LCRT groups, whereas the values of femurs were higher in the LCRT group. The equivalent uniform dose and normal tissue complication probability were higher in the LCRT than the SCRT group for most organs. Treatment complications, including anastomotic leakage, bowel adhesion, and hematologic toxicity, were not significantly different between SCRT and LCRT groups. CIs were 0.84±0.2 and 0.61±0.1 for SCRT and LCRT, respectively. The CVIs were 1.07±0.0 and 1.10±0.1, and the HIs were 0.09±0.0 and 0.11±0.1 for SCRT and LCRT, respectively. The sphincter-saving rates were 89.5% and 94.3% for SCRT and LCRT, respectively. The complete pathologic remission rates were 21.1% and 13.2%, and the down-staging rates were 47.4% and 26.4% for SCRT and LCRT, respectively. SCRT with IMRT is comparable to conventional LCRT in both physical indexes and clinical outcome. The preoperative SCRT, compensated by IMRT, is an effective and safe modality.

Keywords: Chemoradiotherapy, Preoperative treatment, Rectal cancer, Physical Index, Short course

Introduction

Concerns about the complications and lifelong consequences of short-course chemoradiotherapy (SCRT) with delayed surgery for patients with locally advanced rectal cancer led us to verify the correlations between clinical outcomes and physical factors of intensity modulation radiation therapy-based SCRT compared with those of conventional radiotherapy (RT). Conventional preoperative RT, which is the standard treatment for stage II/III rectal cancer patients, takes 6 weeks to complete and normally delivers 50.4 Gy of radiation to the patient. Compared with long-course chemoradiotherapy (LCRT), SCRT takes only a week and delivers approximately 25 Gy, having the dose

and shortening the length of treatment by 6 times. This is important because the longer the treatment duration, the greater the decrease in the patient's strength. Moreover, less radiation is delivered to patients, which is expected to lead to a lower occurrence of radiation-induced complications. Based on research conducted by the Dutch Colorectal Cancer Group and the Swedish Rectal Cancer Trial, short-course radiotherapy can reduce the risk of local recurrence.[1)]

Nonetheless, short-course treatment is not the best treatment option in every aspect. Without sufficient time allowed for tumors to shrink to a more desirable size, there is a smaller chance of pathological complete remission or downstaging after surgery.[2)] Therefore, our institution has adopted concurrent chemoradiotherapy followed by delayed surgery to compensate for the lower probability of pathological complete remission after short-course RT.[3,4)] The 2-year overall survival after SCRT is similar to but lower than that after LCRT, and other clinical indexes including pathological complete remission, downstaging, complications, and sphincter-preserving rate are not significantly different after the two treatment approaches.[5)]

Overall, SCRT is a reasonable and safe option for locally advanced rectal cancer treatment.[6-8)] However, its effectiveness on physical aspects must be validated because the low fractionation number may cause radiation-induced disadvantages. Xiangkui et al. reported that shortening fraction time can harm normal tissues, which have lower DNA repair capacity.[9)] Therefore, unlike the conventional treatment scheme using three-dimensional conformal radiotherapy (3D-CRT), at our institution, short-course treatment is delivered with intensity modulated radiation therapy (IMRT) to spare normal tissue.[10-13)] The aim of this study was to verify the correlations between clinical outcomes and physical factors of short-course chemoradiotherapy (SCRT) and long-course chemoradiotherapy (LCRT) with delayed surgery in rectal cancer patients.

Materials and Methods

Seventy-two patients with rectal cancer who underwent preoperative chemoradiotherapy followed by curative surgery between March 2010 and June 2015 were enrolled. Chemotherapy was a 350 mg/m^2 bolus 5-fluorouracil and 20 mg/m^2 bolus leucovorin (FL) in the first and last week during radiotherapy for LCRT. For SCRT, a 400 mg/m^2 bolus of leucovorin was injected on the 1st day of radiotherapy, and 1200 mg/m^2 of 5-fluorouracil was administered by continuous infusion on the 1st and 2nd days. Between radiotherapy and surgery, 3 cycles of chemotherapy were administered at fortnightly intervals. The treatment type depends on the RT regimen preference of the surgeon, and most outpatients who traveled a long distance to the hospital were given SCRT. The multi-fraction schedule for SCRT and LCRT were 25 Gy in 5 fractions and 50.4 Gy in 28 fractions, respectively. Because it delivers an approximately 3 times higher dose per fraction, SCRT was delivered with an IMRT technique to achieve a dosimetric advantage with normal tissue sparing, while LCRT was conventionally delivered using a 3D-CRT technique. Assuming an alpha-beta ratio of 1, the biologically effective dose (BED)-based prescription dose of SCRT is 53.6 Gy, which is comparable to the prescription dose of LCRT. Patients were treated in the prone position with a belly board. The planning target volume (PTV) and organs at risk (OARs) were contoured according to guidelines of the International Commission on Radiation Units and Measurements Report 50. All plans were created using ECLIPSE version 8.9 software, and calculated results were obtained using a 1 mm grid resolution and AAA dose calculation algorithm. Nine to eleven fields were used in IMRT plans with photon energy of 10MV in most cases, whereas three fields were used in 3D-CRT plans mostly with parallel opposite fields of 10 MV and single Posterior-Anterior (PA) field of 6 MV. In IMRT optimization, dose objectives were set according to the Emami normal tissue tolerance table. For both IMRT and 3D-CRT, plan quality was confirmed before treatment delivery based on the table. Treatments were delivered using a Varian 21iX linear accelerator and Millennium 120-leaf MLC. Curative surgery was performed 8 weeks after completing the CRT schedule in both groups to allow for tumor shrinkage. Adjuvant chemotherapy was routinely recommended 4 weeks after surgery. There were no noteworthy differences in tumor characteristics between the two CRT groups (Table 1).

To examine the correlations between physical factors

Table 1. Patient and treatment plan characteristics.

Factor	Short course (n=19)	Long course (n=53)
Age		
<70	5 (m=73.7)	12 (m=76.8)
≥70	14 (m=58.3)	41 (m=57.6)
Prescribed dose		
Gy	25	50.4
BED		
Gy	150	141
Dose per fraction		
Gy	5	1.8
Normalization		
%	96	96
PTV		
Volume (cm^3)	1109	985
D_{98} (%)	95	93
D_{50} (%)	100	100
D_2 (%)	104	104

LAR, lifetime attributable risk; OED, organ equivalent dose; m, mean value; PTV, planning target volume; $D_{98/50/2}$, dose covering 98%/50%/2% of PTV; BED, Biologically effective dose.

and clinical output, both long-course and short-course radiotherapy plans were analyzed. The OARs were left and right femoral heads, bladder, and bowel. Rectal dermatitis, colitis, and bloody excrement were typical acute complications of rectal cancer RT, and most patients recovered several weeks after completing treatment. There also are chronic side effects such as secondary radiation-induced cancers, intestinal obstructions, and enterobrosia.

Because life expectancy is increasing yearly and South Korea has the 11th highest life expectancy in the world, life time attributable risk (LAR) was calculated for 19 short-course and 53 long-course radiotherapy plans to verify the lifelong influence of a shortened RT schedule.[14] The ratio of patients enrolled in this study under 70 years to over 70 years was 2.8 and 3.4 in the short-course and long-course treatment groups, respectively. For LAR calculations, the risk from age at exposure up to 110 years was integrated, and an EPA (Environmental Protection Agency) approach was applied. Separate evaluations of LAR were made using both an excess absolute risk model and an excess relative risk model.[15-17] Rectal cancer-specific incidence and mortality rates were based on the Surveillance, Epidemiology, and End Results program of the National Cancer Institute.[18] Different mortality rates were applied depending on sex.

To calculate LAR, an organ equivalent dose (OED) was preliminarily calculated. A plateau dose-response curve was used:

$$\mathrm{OED} = \frac{1}{V}\sum_i V_i \frac{(1-\exp(-\delta D_i))}{\delta}$$

where V is total body volume, V_i is volume element with homogeneous dose, and a different δ of 5.1, 0.26, and 0.096 was applied for the bladder, bowel, and femur, respectively. Thus, OED is proportional to cancer risk because it is a dose-response weighted dose variable.

Excess absolute risk (EAR) and excess relative risk (ERR) were calculated using the OED given above. The ERR represents the ratio of the age-specific increase in cancer rate attributable to a radiation dose divided by the baseline rate, which is associated with the background radiation level, whereas EAR is simply the difference in rates attributable to radiation. EAR and ERR are functions of age and sex and are described as follows:[19]

$$\mathrm{EAR}\,(\mathrm{d,\ s,\ e,\ a})\ or\ ERR\,(d,\ s,\ e,\ a) = \beta_s dexp\,(\gamma e^*)\,({}^{a}/_{60})^{\eta}$$

$$where\ e^* = \frac{\min(e, 30) - 30}{10}$$

β_s, γ, and η varied with the model type. For ERR models, β is the ERR per Sv at age-at-exposure 30 and attained age 60. β varies according to the sex of the patient, and it tends to be larger for women than men; β_s for men/women were 0.63/0.43 for the bowel and 0.5/1.65 for the bladder, respectively. The γ value implies that radiogenic risk of cancer at age e falls for every decade increase in age-at-exposure; γ of the bowel and bladder were both –0.3. η implies that the relative amount of ERR is smaller at the attained age; η of the bowel and bladder were both –0.3. Consequently, ERR decreases with age-at-exposure and attained age. In contrast, for EAR models, η=6 for all OAR except for the bowel (η=2.8) and γ=–0.41 for all OAR. Thus, EAR decreases with age-at-exposure but increases with attained age.

Effective uniform dose (EUD) facilitates analysis of dose inhomogeneity within an organ volume by assuming uniform dose distribution in organs. EUD was analyzed for both planning target volume (PTV) and OARs. EUD-based

normal tissue complication probability (NTCP) was also calculated for OARs using the Niemierko model:[20]

$$NTCP=1/(1+(\frac{TD_{50}}{EUD})^{4\gamma_{50}})$$

where TD_{50} is tolerance dose for the 50% complication rate at a specific time interval when the whole OAR is homogeneously irradiated, and γ_{50} is a unitless model parameter that is specific to the normal structure or tumor of interest.

Conformity index ($CI=V95^2_{PTV}/V_{PTV}\times V95$), homogeneity index ($HI=|D_2-D_{98}|/D_{50}$), and coverage index ($CVI=V95_{PTV}/V_{PTV}$) were calculated for PTV to describe the accordance of the 95% isodose line and the PTV contour, the uniformity of dose distribution in PTV, and the PTV volume receiving more than 95% of the prescribed dose, respectively.

Toxicity was scored according to the National Cancer Institute Common Terminology for Adverse Events version 3.0.

Results

Table 2 shows the clinical output, physical factors, and *P* values for LAR, OED, EUD, NTCP, CI, CVI, HI, local recurrence, complete remission, and distant metastasis for both SCRT and LCRT. The OED values of the LCRT group were 1E-01±8E-02 Gy, 2E-01±1E-02 Gy, 0.64±0.88 Gy, and 0.64±0.88 Gy for bowel, bladder, left femur, and right femur, respectively. The OED values of the short-course group were 1E-01±7E-02 Gy, 2E-01±1E-02 Gy, 0.45±0.11 Gy, and 0.44±0.11 Gy in the same order. Because OED is proportional to LAR, LAR has a similar tendency to OED in that bowel and bladder values are similar between the short- and long-course groups and femurs have larger values in the long course group. For the long-course group, LAR was 3E+02±3E+02, 4E+02±3E+01, 21.89±29.80, and 21.76±29.77 for bowel, bladder, left femur, and right femur, respectively. The LAR values of the short-course group were 3E+02±2E+02, 4E+02±2E+01, 15.45±3.90, and 15.07±3.68 in the same order (Table 2).

EUD was relatively higher for LCRT than SCRT in most organs except the bowel, as shown in Table 2. EUD values of the left femoral head, right femoral head, bladder, and bowel were 17.5±3.7 Gy, 17.1±3.3 Gy, 26.7±5.8 Gy, and 5.6±3.9 Gy, respectively, in the short-course CRT group and 22.8±9.4 Gy, 22.3±8.9 Gy, 27.8±11.6 Gy, and 4.5±4.3 Gy in the long-course CRT group. The bowel had a 1.1 Gy higher uniform dose in the short-course group. Overlapping vol-

Table 2. Dosimetric factors and clinical outcomes according to radiation group.

factor	Short course (n=19)	Long course (n=53)	*P*
LAR			
Bladder	4E+02	4E+02	0.294
Bowel	3E+02	3E+02	0.248
LT Femur	15.45	21.89	0.235
RT Femur	15.07	21.76	0.235
OED			
Bladder	2.E-01	2.E-01	0.303
Bowel	1E-01	1E-01	0.242
LT Femur	0.45	0.64	0.235
RT Femur	0.44	0.64	0.235
EUD (Gy)			
Bladder	26.75	27.83	0.248
Bowel	5.59	4.47	0.254
LT Femur	17.51	22.84	0.236
RT Femur	17.05	22.26	0.241
NTCP (%)			
Bladder	5E-07	6E-06	0.305
Bowel	5E-13	1E-10	0.241
LT Femur	8E-09	5E-05	0.357
RT Femur	4E-09	4E-06	0.280
CI			
PTV	0.84	0.61	0.302
CVI			
PTV	1.10	1.07	0.415
HI			
PTV	0.09	0.11	0.645
Local recurrence			0.442
Yes	1	12	
No	18	41	
Complete remission			0.465
Yes	4	7	
No	15	46	
Distant metastasis			0.162
Yes	1	12	
No	18	41	

LAR, lifetime attributable risk; OED, organ equivalent dose; EUD, effective uniform dose; NTCP, normal tissue complication probability; CI, conformity index; CVI, coverage index; HI, homogeneity index.

umes between bowel-PTV and bowel-volume covered by the prescription percentage dose were 46.2±56.4 cm^3 and 43.6±58.6 cm^3, 49.0±5.05 cm^3, and 61.0±61.8 cm^3 for the short- and LCRT groups, respectively. The general limitations for the entire femoral head, bowel, and bladder proposed by Emami et al. are D100 (defined as minimum dose covering 100% of organ volume) <52 Gy, V_{50} (percentage of volume receiving 50Gy) <5%, and V_{50} <50%, respectively; thus, the EUDs of all OARs are below the level considered risky.[21] The SCRT group had lower NTCP values in every OAR.

NTCP values for the left femoral head, right femoral head, bladder, and bowel were 8E-09±1E-08, 4E-09±7E-09, 5E-07±9E-07, and 5E-13±2E-12, respectively, in the SCRT group and 5E-05±3E-04, 4E-06±1E-05, 6E-06±1E-05, and 1E-10±8E-10 in the LCRT group. CIs were 0.84±0.2 and 0.61±0.1 for the SCRT and LCRT groups, respectively, and CVIs were 1.07±0.0 and 1.10±0.1. Because variance less than 1 is desirable for both CI and CVI, SCRT has a relatively better tendency compared to the conventional 3D-CRT technique LCRT, but the difference is minimal when considering the error. HI, with an ideal value of zero, was 0.09±0.0 and 0.11±0.1 for the SCRT and LCRT groups, respectively.

Complete remission was observed in 4 (21.1%) SCRT cases and 7 (13.2%) LCRT cases. Downstaging was observed in 9 (47.4%) SCRT cases and 14 (26.4%) LCRT cases. Negative circumferential resection margin was observed in 17 (89.5%) SCRT cases and 47 (88.7%) SCRT cases. There was 1 (5.3%) SCRT case after 28 months and 1 (1.9%) LCRT case after 9 months with locoregional recurrence. There was 1 (5.3%) SCRT case and 12 (22.6%) LCRT cases with distance metastasis (DM). The 2-year disease-free-survival (DFS) rate was 93.8% in the SCRT group and 74.0% in the LCRT group. Twenty year overall survival (OS) was 90.0% with SCRT and 91.2% with LCRT. Two patients died at 22 months and 39 months after SCRT. Four patients were dead at 24 months after LCRT, and 1 patient died at 52 months. With SCRT, 1 patient (5.6%) experienced grade 4 anastomosis site leakage requiring surgical intervention, 1 (5.6%) patient experienced grade 3 hematologic toxicity and bowel adhesion, and 3 (16.7%) patients experienced grade 3 anastomosis site leakage toxicity. In LCRT, 1 (1.9%) patient experienced grade 4 anastomosis site leakage, 1 (1.9%) patient experienced grade 3 diarrhea toxicity and bowel adhesion, and 5 (9.4%) patients experienced grade 3 anastomosis site leakage.

Discussion

The aim of this study was to verify the correlations between clinical outcomes and physical factors of SCRT and LCRT with delayed surgery in patients with rectal cancer. In a previous clinical study, preoperative SCRT and delayed surgery for locally advanced rectal cancer were confirmed to have clinical effectiveness comparable to that of conventional CRT. In accordance with the results of that previous study, this study supports the rationality of SCRT for rectal cancer treatment in terms of physical aspects.

In this study, we found that SCRT with delayed surgery led to pathologic response and down staged rates comparable to those of LCRT for patients with stage II or III rectal cancer. Physical factors for targets such as BED-based prescription dose, CI, CVI, and HI were also found to be consistent with clinical outcomes.

When patients of the SCRT group were treated with the IMRT technique, the average LAR of femurs was lower than that in patients of the LCRT group, and the average LARs of bowel and bladder were similar to that of patients in the LCRT group. This difference in LARs is because of the diverse angle distribution and multi-leaf collimator movement of IMRT that leads to higher conformity of the prescribed dose to the tumor volume, resulting in low dose irradiation to OARs. In other words, the dosimetric superiority of IMRT over 3D-CRT may compensate for the potential radiological disadvantages of SCRT. Compared with the conventional treatment scheme, half of the prescription dose is delivered on a 1/6 timescale in SCRT. This comparatively intensive dose delivery may have radiological disadvantages. The correlations between clinical outcomes and LAR in SCRT and LCRT are difficult to identify at this stage because of the longer follow-up period and large amount of statistically significant patient data required.

Bowel EUD was relatively higher with SCRT, although the other OARs had smaller EUD values than LCRT. Meanwhile, EUD-based NTCPs were smaller with SCRT for all

OARs. Because of certain dosimetric characteristics of the bowel, partial high dose irradiation has a greater risk for radiation-induced complications, such as enterobrosis, than low dose irradiation.

Other OARs for the bladder and femoral heads had lower EUDs and NTCPs in SCRT because these organs are located in the typical 3D-CRT beam route. In conventional long-course 3D-CRT, a three-channel (left lateral, right lateral, post-anterior [PA]) box plan is the general plan for rectal cancer. The femoral heads and bladder are located in the lateral and PA beam routes, respectively. However, in short-course IMRT, the radiation is less concentrated in OARs because the beams are distributed in multiple directions. This enables higher PTV conformity and lower OAR exposure.

Toxicities according to radiation groups are summarized in Table 3. Grade 3 or 4 anastomosis site leakage requiring surgical intervention was noted in 4 (21.1 %) patients with short-course IMRT and 5 (9.4 %) patients with 3D-CRT (P=0.353). Grade 3 or 4 bowel adhesion was noted in 1 (5.3 %) patient in short-course IMRT and 1 (1.9 %) patient in 3D-CRT (P=0.168). In conclusion, toxicities from short-course IMRT did not significantly differ from the clinical outcomes of 3D-CRT. These results are explained in Table 2. Our data showed that, compared to IMRT, the 3D-CRT plan of whole pelvis irradiation did not reduce the LAR, OED, or NTCP.

For the chemotherapy with the radiation treatment in rectal cancer cases, several randomized clinical trials(J Clin Oncol. 2006; 24:4620-4625/ Cancer. 1984; 53:1811-1818/ N Engl J Med. 2006; 355:1114-1123) were conducted that compare preoperative CRT with radiotherapy alone was shown to significantly increase local control. So National Comprehensive Cancer Network guidelines recommends that in patients with locally advanced rectal cancer treated with preoperative radiotherapy, adding fluorouracil based chemotherapy has significant effect with respect to local control.

Table 3. Toxicities according to radiation group.

	Short course (n=19)	Long course (n=53)	*P*
	Grade 3, 4	Grade 3, 4	
Leakage	3 (21.1)	5 (9.4)	0.353
Hematology	1 (5.3)	0 (0.0)	0.391
Adhesion	1 (5.3)	1 (1.9)	0.168

Data are presented as n (%).

However, the benefit of adding chemotherapy to SCRT is not clear. The present study showed superior outcomes, with a downstaging rate of 47.4% and a complete remission rate of 21.1% in the SCRT group and feasible toxicities, with 1 patients experienced grade 3 hematologic toxicity in the SCRT group. So, we elicit that concurrent chemotherapy with SCRT and an additional 3 cycles of chemotherapy before surgery may be able to consolidate treatment.

Conclusion

SCRT with IMRT is slightly better or comparable to conventional LCRT in both physical indexes and clinical outcome. Preoperative short-course CRT, compensated by IMRT, is an effective and safe modality.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

Ethics Approval and Consent to Participate

The study was approved by the institutional review board (IRB approval number; 2015-12-016).

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