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Physical effects of *Anma* therapy (Japanese massage) for gynecologic cancer survivors: A randomized controlled trial☆

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HIGHLIGHTS

- This is the first randomized controlled trial on the effects of *Anma* therapy (Japanese massage).
- *Anma* therapy reduced subjective physical complaints in gynecologic cancer survivors.
- It is possible that *Anma* therapy inhibits the sympathetic nervous system.

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ABSTRACT

Objectives. Cancer survivors often have physical and psychological complaints after standard cancer treatment. We conducted a randomized control trial to evaluate the physical and psychological/emotional effects of *Anma* therapy (Japanese massage, AMT) in gynecologic cancer survivors. The primary objective was to verify the effects of 8 consecutive weeks of weekly AMT. The secondary objective was to confirm the immediate effects of single-session AMT. We report here results of the physical effects of AMT.

Methods. Forty participants were randomly allocated to an AMT group that received one 40-min AMT session per week for 8 weeks and a no-AMT group. The primary endpoint was severity of subjective physical complaints assessed using a visual analogue scale (VAS). Secondary endpoints were urine and saliva analyses and psychological/emotional questionnaire scores.

Results. In the primary analysis, least-squares means (LSM) estimates of VAS score improvement over the 8 weeks were −21.5 (95% confidence interval [CI], −30.1 to −12.8, P = 0.0017) in the AMT group (n = 20) and 0.8 (95%CI, −7.7 to 9.2, P = 0.89) in the no-AMT group (n = 20). The difference in the LSM estimates between the groups was −22.2 (95%CI, −34.4 to −10.1, P = 0.0007). There were significant differences in VAS score and urinary epinephrine between before and after the intervention session, demonstrating the superiority of AMT.

Conclusions. A single AMT session reduces the severity of subjective physical complaints and might inhibit the sympathetic nervous system in gynecologic cancer survivors. Receiving weekly AMT sessions for eight weeks effectively continues to reduce the severity of subjective physical complaints.

1. Introduction

Cancer has been the leading cause of death in the Japanese population since 1981. Average yearly estimates for the period 2025–2029 put the number of cancer deaths at 230,000 men and 160,000 women and cancer incidence at 530,000 men and 390,000 women in Japan [1]. Both these estimates are expected to slow after 2015 for men; however, they are expected to continue increasing at the present rate for women, especially with regard to incidence of cancers in the oral cavity and pharynx, kidney and urinary tract, uterus, lung, pancreas, and cervix

☆ Trial registration: This trial was registered with the UMIN Clinical Trials Registry as application UMIN000009097 on October 12, 2012: Effects of continuous traditional Japanese massage therapy (*Anma* therapy) for cancer survivors: a randomized controlled trial, https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000010670&language=E.

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[1]. Also, because early detection and progressive treatment options have improved the prognosis of cancer patients and increased the number of cancer survivors in Japan [2], interest has been shifting from radical treatment options toward ensuring a better quality of life (QOL) to cope with the disease [3].

Massage therapy is one of the most commonly used complementary and alternative medicines for cancer patients and survivors to manage physical, emotional, and psychological complaints. In relation to gynecologic cancers, Mirabeau-Beale et al. revealed that massage is one of the most commonly used modalities by ovarian cancer survivors primarily to improve QOL [4]. Also, according to Matulonis et al., of the 22.4% of ovarian cancer survivors who used massage to treat their cancer, 100% used it to improve QOL, 61.5% used it to improve side effects, and 15.4% used it for movement and physical therapy [5]. Actually, 20% of ovarian cancer survivors have reported long-term side effects of treatment, including problems related to abdominal and gynecologic symptoms and neurotoxicity [6]. Ovarian cancer survivors have also reported significant concerns related to pain and other complaints [7].

One of the most common and popular forms of complementary and alternative medicine in Japan is Japanese massage therapy, or *Anma* massage therapy (AMT). It has long been used by healthy persons, the elderly, disease-free survivors, patients with disease, and cancer survivors to promote health, manage and cure various complaints, and prevent disease. However, because the effectiveness of AMT has not been established for cancer survivors and patients, they must determine for themselves, based solely on anecdotal information, whether or not to receive AMT. To address this situation, scientific studies on AMT are needed.

After conducting a preliminary study for cancer survivors who had undergone surgery for uterine cervical or endometrial cancer (FIGO stage Ia1 – Iia) and verifying the effects of AMT [8], based on our preliminary findings we designed and conducted the present randomized controlled trial. The design has been published previously [9]. The primary objective of this trial was to verify physical and psychological/emotional effects of 8 consecutive weeks of weekly AMT in gynecologic cancer survivors. The secondary objective was to confirm the physical and psychological/emotional immediate effects of single AMT intervention session.

Our hypotheses were that AMT for gynecologic cancer survivors would: (H1) improve more subjective physical complaints appearing after standard cancer treatment than in controls immediately after a single intervention session, and these effects would be sustained by 8 consecutive weeks of once-weekly AMT sessions; (H2) enhance psychological and mood states more so than in the controls; (H3) potentially improve coping styles in cancer survivors through the relationship with a massage therapist; and (H4) change the values of some kinds of biochemical markers related to stress release, the autonomic nervous system, or the immune system.

2. Methods

This trial was approved by the Medical Ethics Committee of Tsukuba University of Technology, Japan, where the study setting and coordinating office were located, on September 27, 2012 (Approval No. 5).

Trial gynecologists who worked at another hospital recruited participants who met the eligibility criteria, and they confirmed at every clinical session that participants did not fall into the exclusion criteria. Trial inclusion criteria were: (a) histologically confirmed uterine cervical, endometrial, ovarian, fallopian tubal, or peritoneal cancer in the past; (b) no recurrence of such cancer for ≥3 years since finishing standard medical treatment; (c) ≥20 years of age at the date of registration to the trial; and (d) eligibility for the trial confirmed by gynecologists responsible for the patient. Trial exclusion criteria were: (a) current active infection(s); (b) serious concurrent disease of the heart, liver, or kidney; and (c) severe mental disorder(s). Next, the gynecologists sent introduction forms by facsimile to the coordinating office. After receipt, the coordinating office scheduled a meeting date with each cancer survivor to provide them with trial information (oral and written) at the coordinating office. Patients subsequently submitted a consent form to participate in the trial by hand or via facsimile.

After finishing enrolment, randomization was performed. The trial statistician generated the allocation sequence by block randomization. However, allocation adjustment factors were not set in the trial due to currently insufficient evidence on factors influencing the effectiveness of AMT. Before the trial began, the trial statistician created a table of randomized assignment for management by 2 employees at the coordinating office.

2.1. AMT group

This group received treatment by AMT. Protocol treatment was completed once the participant finished receiving the eighth and final 40-min AMT session. Sessions were given once a week during the consecutive 8-week intervention period. Following the AMT protocol, participants were given a full body AMT session that excluded the face, head, and abdomen while lying on a massage table. We conducted assessments before the first AMT session (pre-session, baseline), after the first AMT session (post-session), and before the last (8th) AMT session (8-week follow-up).

2.1.1. AMT protocol

First, the massage therapist interviewed the participant about subjective physical complaints appearing after standard cancer treatment and then manually checked the affected area(s) for muscle tension, stiffness, induration, tenderness, knocking pain, malalignment of the spine, edema, and area of pain/discomfort/palsy, and other such conditions. Second, while the participant lay on the right side of the body on a massage table, the left side of the body was massaged. The massage started at the upper shoulder and then moved to the back, lower back, upper limb (shoulder joint to wrist joint), hand (carpus to finger tips), and neck (superior nuchal line along the neck to the side of the 7th cervical vertebra). The massage then returned to the trunk (shoulder to lower back) following these areas: buttock, lower limb (gluteal fold to ankle joint), and foot (heel to toes). Third, while the participant was lying on the left side, the opposite side of the body was massaged in the same order. Finally, while the participant was lying in a prone position, the massage was repeated briefly on the shoulders, back, lower back, lower limbs, and feet simultaneously on both sides. During the massage, the therapist focused the massage on specific locations related to the participant's physical complaints. This massage procedure was the same as that used in our previous studies [8,10], using massage techniques considered standard versions of common AMT and as described in detail by Kimura [11]. AMT mostly targets the muscles by kneading (thumb, 2-finger [thumb and forefinger], 4-finger, carpus, palm, and palm grasp), which is the most commonly used technique. Thumb kneading is most frequently used, followed by pressing (thumb, carpus, and palm), and then with lesser amounts of stroking (2 hands, thumb, and fingertips). AMT is performed through the clothing, with stimulation intensity applied according to each patient's range of comfort. A therapist with a national massage practitioner license from Japan and >20 years of experience performed all massage sessions to avoid differences in technical capabilities.

2.2. No-AMT group

The control group was followed as usual by their medical doctors and did not receive AMT treatment. They met with the massage therapist at the coordinating office on the first day of their scheduled trial period to receive a 40-min semi-structured chat intervention with no massage while seated. Assessments were conducted before the intervention session (pre-session, baseline) and after the intervention session (post-session). Participants returned to the office on the last day

of their 8-week trial period for another assessment (8-week follow-up), after which they received a single 40-min AMT session as a gift for participating in the study.

2.2.1. Chat protocol and chat policy

The semi-structured chat protocol was designed to facilitate natural and relaxed conversation that was positive and honest. First, as with the AMT group, the massage therapist conducted an interview and checked by hand the participant's physical condition after standard cancer treatment. Second, to enhance self-disclosure or willingness to reveal personal information to others, the therapist interviewed the participant stating, "You've had a huge experience, getting a diagnosis of cancer and then making it through cancer safely. Could you tell me what you felt, what you thought, what you did at the time, and anything else you would like to add?" All participants had much to say about their memories and thoughts. Next, to facilitate positive thinking, the therapist asked, "Have you had any happy or pleasant things happen to you recently, and could you tell me about them?" The therapist paid full attention and repeated the participant's words with the same emotional expression. At the end of the session, using a positive feedback method, the therapist repeated what she felt were the most emotionally impactful words spoken by the patient, shared her feelings about the participant's words, and then empathized with the participant.

2.3. Outcomes

2.3.1. Primary outcome measure

The primary outcome measure was the change in severity of subjective physical complaints appearing after standard cancer treatment, determined using a visual analogue scale (VAS). The VAS was a sheet of paper with a 100-mm line from left (no physical complaint) to right (worst imaginable physical complaint). Participants were asked to indicate the severity of their physical complaint at the time by placing a tick on the line, and length from the left side to the tick was measured and used as the VAS score. Scores ranged from 0 to 100, with higher score indicating more severe degree of physical complaint.

2.3.2. Secondary outcome measures

Secondary outcome measures included biochemical measures and self-administered questionnaires.

2.3.2.1. Biochemical measures. Urine samples were provided to assay concentrations of epinephrine, norepinephrine, dopamine, and 8-hydroxydeoxyguanosine (8-OHdG). Saliva samples were also taken to assay concentrations of chromogranin A (CgA), cortisol, and secretory immunoglobulin A (s-IgA). Salivette® (Sarstedt, Aktiengesellschatt & Co., Germany), was used to take 2-mL saliva samples. Briefly, a swab was removed from the Salivette, chewed 120 times gently for two minutes in synch with a metronome, then returned to the device.

2.3.2.2. Self-administered questionnaires. To clarify the effects on psychological/mood status, coping style with cancer, and QOL, we used the following instruments.

(1) Hospital Anxiety Depression Scale, Japanese Version (HADS)
(2) Profile of Mood States - Brief Japanese Version (POMS)
(3) Measure of Adjustment to Cancer, Japanese version (MAC)
(4) Japanese version of the European Organization for Research and Treatment of Cancer QLQ-C30 version 3.0 (EORTC QLQ-C30)

2.4. Data collection

The HADS, MAC, and EORTC QLQ-C30 were administered pre-session and at the 8-week follow-up. The VAS and POMS were administered pre-session, post-session, and at the 8-week follow-up. Urine and saliva samples were also taken pre-session, post-session, and at the 8-week follow-up. Immediately after finishing interventions, urine and saliva samples were frozen and taken to a clinical laboratory testing company the next morning (SRL Inc., Tsukuba branch, Tsuchiura, Japan) for assaying. To avoid alteration of quantities of biochemical materials by the circadian rhythm, all measurement sessions began at 14:30. Fig. 1 shows the timing of sample and questionnaire collection in detail.

2.5. Statistical methods

Based on our preliminary data [8], we assumed that the mean difference would be −20.8 in the AMT group, unchanged (e.g., 0) in the no-AMT group, and that the standard deviation would be 19.6 in both groups. To test these differences between the two groups using a 5% Type I error rate and 90% power, we needed a sample size of 14 participants per group. Based on sensitivity analyses for sample size calculation, the planned sample size was determined to be 30 participants per group [9]. Although the present sample size did not reach the planned sample size, sufficient power for primary analysis was acquired.

We performed all efficacy analysis according to the modified intention-to-treat principle, which included all participants who received at least one AMT session in the AMT group and one chat session in the no-AMT group. Additionally, we performed as-treated analyses, in which participants were classified according to the treatment actually received (not shown).

The primary endpoint was VAS score improvement over the 8-week trial period. For primary analysis, we used the analysis of covariance to compare mean changes in VAS score over the 8 weeks between the AMT group and the no-AMT group, adjusting for baseline VAS score and age. We used a two sample *t*-test with Satterthwaite's approximation to compare mean changes and the paired *t*-test to evaluate mean changes in VAS score for each group. For these mean VAS score changes and their differences, we also calculated two-sided 95% confidence intervals (CIs) to evaluate clinical effects.

For the secondary endpoints, we did not consider multiplicity issues. In all analyses, categorical variables are described in terms of frequency and percentage. The distributions of continuous variables are described using means, standard deviations (SDs), medians, quartiles, and ranges. The Wilcoxon signed-rank test or the Mann-Whitney *U* test was used for non-normally distributed data. Pearson's chi-square test was used to test differences in categorical variables. All reported P-values are two-sided, and all significance levels were set at 0.05. SAS 9.3 (SAS Institute, Cary, NC, USA) was used for all analyses.

3. Results

The start date for recruitment was October 13, 2012. The first participant's trial began on November 2, 2012 and the 8-week follow-up of the 40th participant concluded on November 1, 2014. In this article, we present the results for the physical effects of AMT as change in VAS score as the primary endpoint and change in biomarker levels to verify (H1) and (H4). The results for the psychological/emotional effects, discussed in relation to (H2) and (H3), will be reported separately.

3.1. Baseline characteristics

Fifty-eight participants were eligible for the study and 40 participants submitted the consent form and were enrolled (Fig. 2). Twenty participants were randomized to the AMT group and 20 to the no-AMT group (median age, 53.0 and 55.5 years; median age at cancer onset, 42.5 and 43.5 years; median duration from onset, 8.3 and 8.6 years, respectively) (Table 1). One participant was randomized to the no-AMT group but actually received AMT intervention. Thus, 21

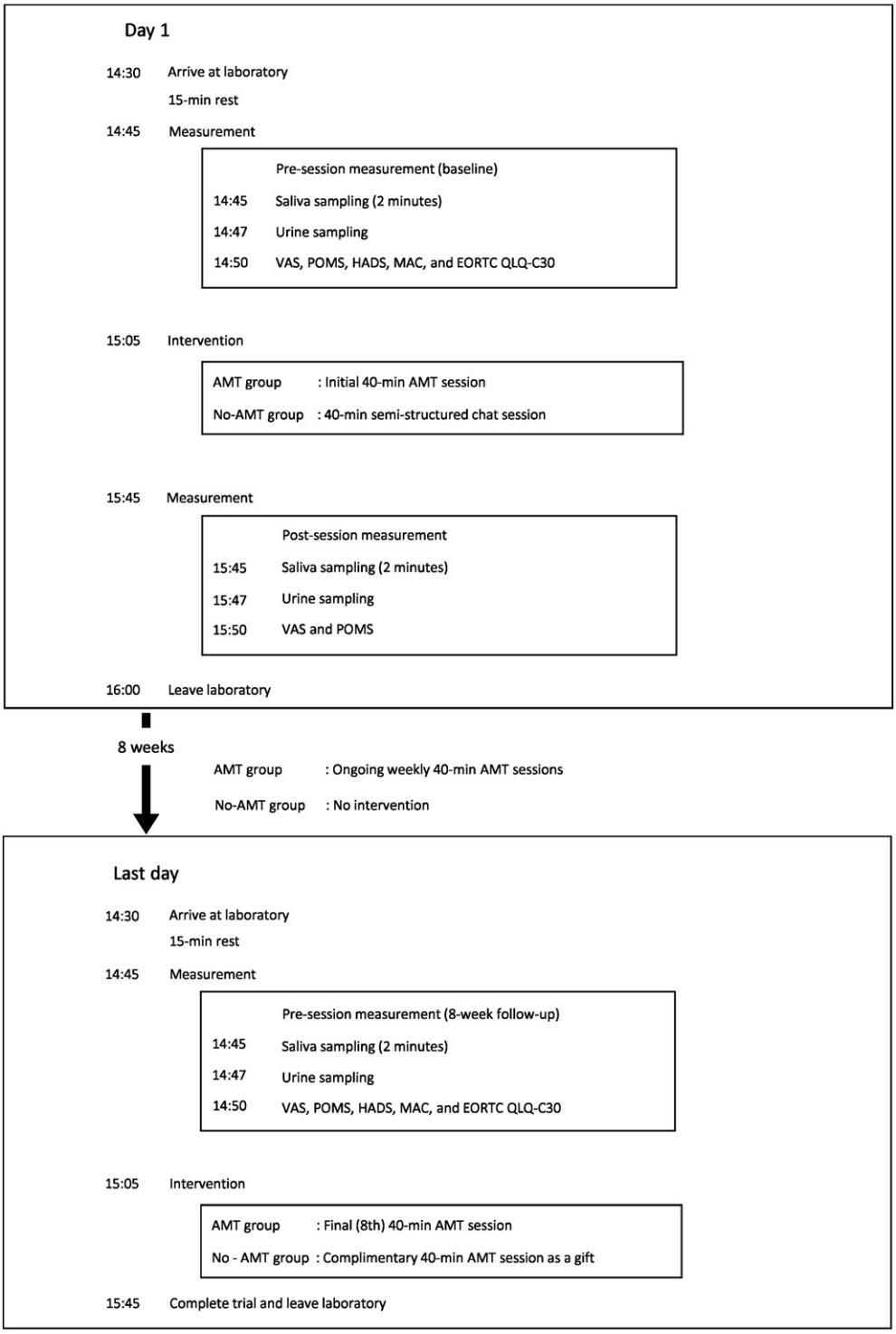

Fig. 1. Intervention and measurement procedure.

participants actually received AMT and 19 received no-AMT. All participants completed their interventions.

Twenty-five (62.5%) participants had uterine cervical cancer, 10 (25.0%) had endometrial cancer, and 5 (12.5%) had ovarian cancer. Seventy percent of participants had stage I cancer. Surgery was undertaken in 37 (92.5%) participants and lymph node dissection in 30 (75.0%). Eleven participants (27.5%) had received chemotherapy and 13 (32.5%) had received radiation therapy. Sociodemographic and clinical variables revealed no significant differences between the AMT and no-AMT groups (Table 1).

3.2. VAS score

In the primary analysis, least-squares mean (LSM) estimates of VAS score improvement over the 8-week trial period were −21.5 (95%CI, −30.1 to −12.8, P = 0.0017) in the AMT group and 0.8 (95%CI, −7.7 to 9.2, P = 0.89) in the no-AMT group. The difference in the LSMs between the two groups was −22.2 (95%CI, −34.4 to −10.1, P = 0.0007), demonstrating the superiority of AMT. A statistical difference in the LSMs was also observed in the supportive as-treated analysis (LSM [95%CI], 23.3 [−35.2 to −11.4], P = 0.0003). Mean improvement

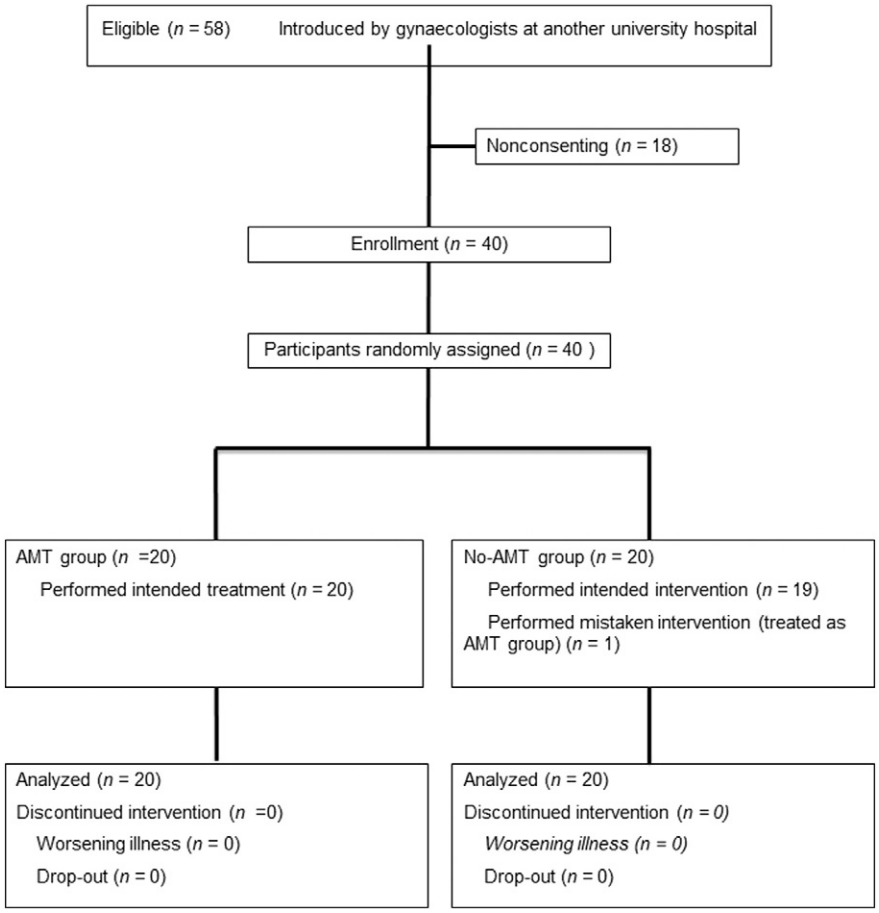

Fig. 2. CONSORT flowchart of participant recruitment.

Table 1
Demographic and clinical characteristics of cancer survivors.

Characteristic	AMT (n = 20)	No AMT (n = 20)	P value
Age, median (min-max)	53.0 (40–69)	55.5 (41–75)	0.60†
Age at cancer onset, years, median (min-max)	42.5 (33–59)	43.5 (26–70)	0.68†
Duration from cancer onset, years, median (min-max)	8.3 (3.1–21.3)	8.6 (3.2–27.8)	0.80†
Site of gynecologic cancer			
Uterine cervix	11 (55%)	14 (70%)	0.34††
Endometrium	7 (35%)	3 (15%)	
Ovary	2 (10%)	3 (15%)	
FIGO stage			
I	13 (65%)	15 (75%)	0.73††
II–IV	7 (35%)	5 (25%)	
Surgery			
Yes	20 (100%)	17 (85%)	0.23††
No	0 (0%)	3 (15%)	
Lymph node dissection			
Yes	16 (80%)	14 (70%)	0.72††
No	4 (20%)	6 (30%)	
Chemotherapy			
Yes	6 (30%)	5 (25%)	1.00††
No	14 (70%)	15 (75%)	
Radiotherapy			
Yes	8 (40%)	5 (25%)	0.50††
No	12 (60%)	15 (75%)	

AMT: *Anma* therapy.
† P value calculated using the Mann-Whitney *U* test.
†† P value calculated using Pearson's chi-square test.

between the pre- and post-session VAS scores was −31.8 (95%CI, −41.1 to −22.4, P < 0.0001) in the AMT group and −7.2 (95%CI, −11.9 to −2.5, P = 0.0045) in the no-AMT group. The difference in the means between the two groups was −24.6 (95%CI, −34.7 to −14.3, P < 0.0001), indicating the immediate efficacy of AMT (Table 2).

3.3. Biomarkers

Between the two groups, a significant difference was found during the 8-week trial period in salivary CgA (median difference, 0.6 in AMT and −1.2 in no-AMT, P = 0.025). Moreover, significant differences in pre- and post-session levels were found in urinary epinephrine (median difference, −1.5 in AMT and 5.1 in no-AMT, P = 0.0011), norepinephrine (median difference, −21 in AMT and 37 in no-AMT, P = 0.0048), and dopamine (median difference, −131 in AMT and 168 in no-AMT, P = 0.010). In the AMT group, a significant decrease was found between the pre- and post-session levels of epinephrine (P = 0.0018). In the no-AMT group, significant increases were seen in epinephrine (P = 0.014), norepinephrine (P = 0.033), and dopamine (P = 0.030) and a significant decrease was seen in CgA (P = 0.0046) (Table 2).

4. Discussion

The results of the primary outcome, namely significant changes in VAS score, indicate the severity of subjective physical complaints appearing after standard cancer treatment. Therefore, hypothesis (H1) was verified. In a review of the physiological and therapeutic effects of massage, Goats found that effects of forceful massage on increased local blood flow were longer lasting than those of gentle pressure and represented a potent means to accelerate healing, and that massage

Table 2
Changes in physical outcomes (modified intention-to-treat population).

Visual analogue scale (VAS)	AMT		No AMT		P value
	N	Mean (SD)	N	Mean (SD)	
Pre-session	20	50 ± 23	20	50 ± 19	−24.6 (−34.7 to −14.3) <0.0001***††
Post-session	20	18 ± 16	20	43 ± 22	
Change from pre-session mean (95%CI)	20	−31.8 (−41.1 to −22.4)	20	−7.2 (−11.9 to −2.5)	
P value†		<0.0001***		0.0045**	
8-week follow-up	20	30 ± 25	20	51 ± 20	−22.2 (−34.4 to −10.1) 0.0007***§
8-week change LSM (95%CI)§	20	−21.5 (−30.1 to −12.8)	20	0.8 (−7.7 to 9.2)	
P value†		0.0017**		0.8860	
Biomarkers	**AMT**		**No AMT**		**P value††**
	N	Median (quartiles)	N	Median (quartiles)	
Urinary epinephrine μg/L					
Pre-session	20	11.5 (6.5 to 23.7)	20	7.0 (4.9 to 12.9)	0.0011**
Post-session	20	7.4 (3.5 to 18.9)	20	11.4 (7.8 to 15.6)	
Change from pre-session	20	−1.5 (−5.4 to −0.2)	20	5.1 (0.3 to 9.0)	
P value†		0.0018**		0.0140*	
8-week follow-up	20	9.4 (4.6 to 12.9)	20	6.4 (4.7 to 12.7)	
8-week change	20	−0.9 (−8.2 to 1.3)	20	−0.5 (−4.7 to 3.8)	0.3993
P value†		0.2731		0.8052	
Urinary norepinephrine μg/L					
Pre-session	20	125 (50 to 193)	20	100 (37 to 137)	0.0048**
Post-session	20	81 (55 to 161)	20	113 (74 to 150)	
Change from pre-session	20	−21 (−43 to 16)	20	37 (18 to 62)	
P value†		0.0973		0.0328*	
8-week follow-up	20	116 (60 to 151)	20	97 (44 to 148)	
8-week change	20	−15 (−86 to 67)	20	5 (−45 to 41)	0.5642
P value†		0.3683		0.7841	
Urinary dopamine μg/L					
Pre-session	20	759 (358 to 1158)	20	503 (204 to 1215)	0.0104*
Post-session	20	596 (425 to 803)	20	635 (445 to 1337)	
Change from pre-session	20	−131 (−452 to 156)	20	168 (62 to 362)	
P value†		0.0826		0.0296*	
8-week follow-up	20	637 (394 to 1500)	20	649 (360 to 1034)	
8-week change	20	−201 (−687 to 369)	20	106 (−179 to 287)	0.3847
P value†		0.3884		0.4304	
Urinary 8-hydroxydeoxyguanosine (8-OHdG) ng/mL					
Pre-session	20	10.6 (9.3 to 14.4)	14	11.4 (9.4 to 13.7)	0.2113
Post-session	19	10.4 (9.0 to 15.6)	20	10.6 (9.7 to 12.7)	
Change from pre-session	19	0.3 (−1.5 to 1.9)	14	−0.6 (−1.5 to 0.5)	
P value†		0.5871		0.0991	
8-week follow-up	18	11.8 (9.7 to 14.4)	17	11.3 (9.1 to 13.0)	
8-week change	18	1.0 (−1.6 to 2.5)	14	−1.1 (−4.8 to 3.1)	0.4420
P value†		0.3987		0.8672	
Salivary chromogranin A (CgA) pmoL/mg protein					
Pre-session	20	3.3 (2.1 to 5.5)	17	3.8 (2.5 to 5.5)	0.0965
Post-session	20	2.7 (2.2 to 4.3)	19	2.9 (1.5 to 6.7)	
Change from pre-session	20	−0.4 (−1.2 to 0.8)	17	−1.2 (−1.7 to −0.6)	
P value†		0.5039		0.0046**	
8-week follow-up	20	3.3 (1.8 to 8.2)	19	3.3 (1.4 to 4.2)	
8-week change	20	0.6 (−1.3 to 1.8)	17	−1.2 (−2.7 to 0.0)	0.0254*
P value†		0.4980		0.0067**	
Salivary cortisol μg/dL					
Pre-session	20	0.07 (0.06 to 0.08)	18	0.08 (0.06 to 0.15)	0.4030
Post-session	20	0.06 (0.06 to 0.07)	19	0.08 (0.06 to 0.12)	
Change from pre-session	20	−0.01 (−0.02 to 0.00)	18	0.00 (−0.02 to 0.00)	
P value†		0.0801		0.2686	
8-week follow-up	20	0.09 (0.06 to 0.13)	19	0.07 (0.06 to 0.12)	
8-week change	20	0.00 (−0.01 to 0.03)	18	−0.02 (−0.06 to 0.00)	0.1605
P value†		0.4716		0.4257	
Secretory immunoglobulin A (s-IgA) μg/mL					
Pre-session	20	281 (170 to 433)	19	299 (205 to 415)	0.9889
Post-session	20	276 (168 to 407)	19	287 (176 to 458)	
Change from pre-session	20	−7 (−123 to 108)	19	−8 (−133 to 70)	
P value†		0.9854		1.0000	
8-week follow-up	20	177 (135 to 281)	19	259 (152 to 356)	
8-week change	20	−56 (−219 to 99)	19	−51 (−212 to 64)	0.7696
P value†		0.5459		0.1819	

has traditionally been used to relieve pain, reduce discomfort, relieve associated muscle spasms, and permit improved function [12]. Also, connective tissue manipulation that manually stimulates skin over the thoracic and lumbar spine triggers cutaneovisceral reflexes that cause vasodilation [12]. The same mechanisms observed in Western massage techniques are thought to operate in AMT. Moreover, by kneading and pressing muscles, muscle spindles are pulled and extended, and that stimulation causes various reflexes, including the stretch reflex and antagonistic inhibition, as well as somatic sensory impulses to travel up to the brain to coordinate muscle function through the neural circuit network. On the way, these afferent neurons undergo changes in the medulla and thalamus, possibly affecting the autonomic nervous system and endocrine/hormonal systems. We suggest that these mechanisms function in AMT to improve various subjective physical complaints in cancer survivors.

According to a literature review by Moraska et al. [13], seven studies have reported data on urinary catecholamines following massage therapy. Five of those studies reported no significant change in epinephrine or norepinephrine over the study duration [14–18]. These results are in line with those of the present study.

Additionally, the present study revealed a significant reduction in epinephrine, but no changes in norepinephrine and dopamine immediately after an AMT session; in contrast, immediately after the chat session, there was a significant increase in norepinephrine and dopamine. Norepinephrine, indeed, may be known as a stress marker; however, it has been reported that norepinephrine may contribute to cognitive function [19,20]. Serotonin & norepinephrine reuptake inhibitors have recently been used to increase serotonin, norepinephrine, and dopamine to treat mood disorders such as depression. These differences between the two groups were significant and suggest that the sympathetic nervous system might be inhibited by AMT and mental activity might be activated [21] by the chat session.

Studies have recently used salivary CgA concentration as a new stress index to reflect the sympathetic nervous system [22,23]. In the present study, both groups showed CgA concentration had decreased post-session compared with pre-session values; however, only the no-AMT group showed a significant reduction, with no significant difference between the two groups. However, at 8 weeks, the reduction remained significant in the no-AMT group, with a significant difference between the two groups. These results suggest that the sympathetic nervous system might also be inhibited in the no-AMT group. According to O'Connor et al. [24], salivary CgA might have the property of not being easily affected by physical stress, which is different from other sympathoneural biomarkers. Thus, Miki suggests that the secretory mechanism of salivary CgA might differ from that of urinary norepinephrine excretion [25]. Based on the present results, epinephrine output might be primarily influenced by physical activity through AMT, whereas CgA might be more responsive to mental activity by the chat intervention. This chat intervention might have dimensions of psychotherapy due to its inclusion of self-disclosure [26,27], positive thinking [28–30], and a positive feedback method. It might possibly act directly on the brain to inhibit sympathetic nervous system activity and sustain the effect longer than physical stimulation.

No significant differences were observed in urinary 8-OHdG (as an oxidative stress marker), salivary cortisol (which becomes synonymous with stress hormone), or s-IgA (which is thought to reflect immune activity).

This was a pilot RCT study on the use of individualized AMT for gynecologic cancer survivors. This study has some limitations. First, the study was conducted in a small city (population 200,000), so the sample size was small. Furthermore, eligibility criteria were very open. Thus, it is difficult to generalize the results from this RCT to the wider effectiveness of AMT for cancer survivors. A subsequent multicenter RCT should be used to verify our findings and recruit a more consistent population, as well as limit the characteristic of the sample population, such as the tumor type, cancer stages, duration from cancer onset, or physical complaint. Second, we should consider what intervention method is appropriate as a control group for AMT. In this study, we used a semi-structured chat, which might include psychotherapeutic dimensions, which made comparison difficult. A subsequent RCT might incorporate non-*Anma* relaxation practices like yoga or meditation for the control group. In addition, we may review more suitable outcome measures, such as interleukin 6 or 10, which may be good candidates for outcomes for AMT. Moreover, AMT is Japanese medical massage that is specifically tailored to a recipients' individual physical and mental state, and this makes it difficult to develop a standard AMT pragmatic protocol because the degree of stimulation must be adjusted to the individual. These limitations might have led to the low levels of evidence in the present study. Nevertheless, our findings can help medical professionals explain the benefits of AMT to gynecologic cancer survivors and provides higher quality information to better inform patients in their decision whether to receive AMT or not.

5. Conclusion

A simple 40-min AMT session reduced the severity of subjective physical complaints and the effect was sustained by continuous once weekly AMT in gynecologic cancer survivors. These results imply that AMT has benefits in oncology.

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Conflict of interest disclosures

The authors declare no competing interests.

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Notes to Table 2:
AMT: *Anma* therapy; CI: confidence interval; LSM: least-squares mean; VAS: visual analogue scale scores.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.
VAS:
† P value calculated using paired *t*-test.
†† P value calculated using a two-sample *t*-test.
§ LSM and P value calculated using analysis of covariance.
Biomarkers:
† P value calculated using Wilcoxon's signed-rank test.
†† P value calculated using the Mann-Whitney U test.

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