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Massage Therapy vs. Simple Touch to Improve Pain and Mood in Patients with Advanced Cancer: A Randomized Trial

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Protocol: Available to interested readers by contacting Dr. Kutner at jean.kutner@ucdenver.edu. Massage and simple touch protocols are available as electronic appendices at annals.org.

Statistical code: Available to interested readers by contacting Dr. Fairclough at diane.fairclough@ucdenver.edu

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Abstract

BACKGROUND—Small studies of variable quality suggest that massage therapy may relieve pain and other symptoms.

OBJECTIVE—Evaluate efficacy of massage for decreasing pain and symptom distress and improving quality of life among persons with advanced cancer.

DESIGN—Multi-site randomized clinical trial.

SETTING—Population-based Palliative Care Research Network (PoPCRN).

PATIENTS—380 adults with advanced cancer experiencing moderate-severe pain; 90% were enrolled in hospice.

INTERVENTION—Six 30-minute massage or simple touch sessions over two weeks.

MEASUREMENTS—Primary outcomes were immediate (Memorial Pain Assessment Card, MPAC, 0 – 10 scale) and sustained (Brief Pain Inventory, BPI, 0 – 10 scales) change in pain. Secondary outcomes were immediate change in mood (MPAC 0 – 10 scale) and 60-second heart and respiratory rates and sustained change in quality of life (McGill Quality of Life Questionnaire, MQOL, 0 – 10 scale), symptom distress (Memorial Symptom Assessment Scale, MSAS, 0 – 4 scale), and analgesic medication use (parenteral morphine equivalents (milligrams/24 hours). Immediate outcomes were obtained just prior to and following each treatment session. Sustained outcomes were obtained at baseline and weekly for 3 weeks.

RESULTS—298 were included in the immediate outcome analysis and 348 in the sustained outcome analysis. 82 did not receive any allocated study treatments (37 massage, 45 control). Both groups demonstrated immediate improvement in pain (massage -1.87 points (CI, -2.07, -1.67), control -0.97 points (CI, -1.18, -0.76)) and mood (massage 1.58 points (CI, 1.40, 1.76), control 0.97 points (CI, 0.78, 1.16)). Massage was superior for both pain and mood (mean difference 0.90 and 0.61 points, respectively, $P < 0.001$). There were no between group mean differences over time in pain (BPI Mean 0.07 (CI, -0.23, 0.37), BPI Worst -0.14 (CI, -0.59, 0.31)), quality of life (MQOL Overall 0.08 (CI, -0.37, 0.53)), symptom distress (MSAS Global Distress Index -0.002 (CI, -0.12, 0.12)), or analgesic medication use (parenteral morphine equivalents -0.10 (CI, -0.25, 0.05)).

LIMITATIONS—The immediate outcome measures were obtained by unblinded study therapists, possibly leading to reporting bias and the overestimation of beneficial effect. The generalizability to all advanced cancer patients is uncertain. The differential beneficial effect of massage therapy over simple touch is not conclusive in the absence of a “usual care” control arm.

CONCLUSIONS—Massage may have immediately beneficial effects on pain and mood among patients with advanced cancer. Given the lack of sustained effects and the observed improvements in both study arms, the potential benefits of attention and simple touch should also be considered in this population.

INTRODUCTION

Symptom relief is central to end-of-life care, however many terminally-ill individuals experience serious pain and other physical and emotional symptoms. (1-4) Studies examining

efficacy of therapies that may mediate these symptoms deserve the highest priority. Research directed at improving care at the end of life has been recommended by the Institute of Medicine and the National Institutes of Health. (5;6)

Pain associated with advanced cancer can cause physical and emotional distress leading to decreased functional ability and quality of life. Massage may interrupt the cycle of distress through therapist intentionality (presence, communication and desire to produce a therapeutic response), induction of a relaxation response, increased blood and lymphatic circulation, potentiation of analgesic effects, decreased inflammation and edema, manual release of muscle spasms, increased endogenous endorphin release and competing sensory stimuli that override pain signals. (7-11) Despite theoretical bases supporting its use and growing acceptance, few randomized clinical trials have assessed the efficacy of massage therapy. Large trials have been difficult to design and carry out; challenges include frailty of late-stage cancer patients and health care provider reluctance to refer because of the possibility of randomization to non-massage therapy control. (12)

Therapeutic massage has potential to reduce pain and improve symptom distress and quality of life for cancer patients at the end of life. The purpose of the “Reducing End-of-Life Symptoms with Touch (REST)” study was to evaluate the efficacy of massage compared to an exposure controlling for time, attention and touch. We hypothesized that massage would decrease pain and explored effects on quality of life, physical and emotional symptom distress and analgesic medicine use.

METHODS

Design Overview

This prospective, 2-group, randomized, single-blind trial was conducted between November 2003 and October 2006. After evaluation for inclusion and exclusion criteria, participants provided written informed consent and were randomly assigned to a treatment group, massage, or control exposure, simple touch. Figure 1 depicts the timing of the study procedures for a hypothetical participant. Individual characteristics, disease, pain characteristics, symptom distress, quality of life, functional status (Karnofsky Performance Scale)(13), expected helpfulness of massage for pain, and concurrent interventions (pharmacologic and non-pharmacologic) were collected at baseline (within 72 hours of study enrollment) and at 3 subsequent weekly visits over the 3-4 week period of participation (sustained outcomes). Final data collection occurred approximately 1 week following the final treatment. Data collectors were blinded to treatment assignment. Participants received up to six 30-minute treatments over two weeks, with at least 24 hours between treatment sessions. The initial treatment session occurred within 48 hours of baseline data collection. Scheduling of treatment sessions was determined by the treatment provider and the patient. Immediate outcomes were obtained just prior to and following every treatment session by treatment providers who were not blinded to treatment assignment. All participants received routine care in addition to the specified interventions. The Colorado Multiple Institutional Review Board and, where applicable, site-specific institutional review boards approved the study.

Setting and Participants

Study sites included fifteen U.S. hospices that are members of the Population-based Palliative Care Research Network (PoPCRN) (14) and the University of Colorado Cancer Center. Eligible participants were English-speaking adults with advanced cancer (stage III or IV, all cancer types, any care setting) who had at least moderate pain (≥ 4 on a 0 – 10 scale) in the week prior to enrollment, anticipated life expectancy of at least three weeks and were able to

consent. Exclusion criteria included receipt of professional massage within one month of enrollment, anticoagulant therapy, known platelet count below 10,000 or known unstable spine.

Randomization and Interventions

Verification of eligibility was forwarded by a study coordinator from each study site to the University of Colorado researchers. Individuals were then randomized centrally by two designated investigators; assignments were transmitted back to the requesting site. All study personnel other than the on-site study coordinators and these two designated investigators were blinded to the randomization sequence. The randomization sequence was generated by a SAS program that produced a randomized block design, stratified by study site. Block size randomly varied between 2, 4 and 6 so that it was not possible to predict the next assignment. To minimize likelihood that potential participants would decline enrollment due to reluctance to be randomized, those assigned to the control arm were offered massage after study completion.

The Experimental Treatment: Massage Therapy—The massage intervention included light/gentle effleurage, petrissage and myofascial trigger point release. Effleurage is a smooth, gliding stroke; petrissage is squeezing, rolling and kneading the muscles. Trigger point release provides concentrated finger pressure to painful localized areas in muscles to break cycles of spasm and pain. (15) Individual therapist judgment dictated the rhythm/rate/stroke frequency, sequence/mix of strokes, time spent in each stroke, stroke length and body area massaged. (16) Therapists spent 65% of the time in effleurage and 35% in petrissage. The most frequently massaged areas of the body were the neck and upper back (about 80% of the time) and arms, hands, lower legs, and feet (about 75% of the time). Other areas, such as the chest, abdomen, buttocks, back of the thighs and forehead were massaged less than 50% of the time. Massage was appropriately modified in persons with skin fragility, postural limitations, edema, osteoporosis or bone metastasis. Sites of inflammation/infection, hyperesthesias, injury, surgery, ports, catheters, deep vein thrombosis and tumors were avoided. Therapists identified and treated up to 3 myofascial trigger points per session (located 15-25% of the time in the neck, upper trapezius, and lower trapezius regions). Half of the sessions were provided with the patient supine; 25% seated and the remainder split between side-lying and prone positions. Temperature and level of privacy varied with setting. Less than 25% of participants were unclothed during treatments. Massage was performed by licensed massage therapists who had at least 6 months experience treating advanced cancer or hospice patients and completed a minimum 500-hour program of study in massage from an institution recognized by their state as a vocational school.

The Control Exposure—The control exposure, simple touch, was designed to control for the *time, attention, touch* and *healing intent* components of the intervention. (17) The control consisted of placement of both hands on the participant for 3 minutes at each of the following locations bilaterally: base of neck, shoulder blades, lower back, calves, heels, clavicles, lower arms, hands, patellae, and feet. Pressure was light and consistent, with no side-to-side hand movement. Control therapy providers interrupted conscious healing intention by silently counting backwards from 100 by 7s, reciting nursery rhymes, or planning their day's activities. (18;19) The control treatments were provided by individuals with no prior body or energy work experience.

All treatment providers participated in standardized hands-on training, received a study manual and training video and were evaluated for competency in study procedures. Adherence to study protocols was monitored during twice-yearly site visits. Treatment providers in both groups used Biotone brand hypoallergenic unscented massage crème. For the purposes of standardization and to mediate the presence of intervening variables, music, essential oils and energy work were not permitted and treatment providers were instructed to limit their

communication to providing instructions or responding to therapy-related questions. To minimize variation by treatment provider, one primary massage therapist or simple touch provider per participant at each study site administered study treatments.

Outcomes and Follow-up

All study data were collected by face-to-face interviewer-administered questionnaires.

Neuropathic pain was measured at baseline only by the Neuropathy Pain Scale (NPS, 0 – 10 scale), which is sensitive to pain qualities most common to neuropathic pain syndromes. (20; 21) Presence of neuropathic pain was defined as NPS summary score greater than 3.

Primary Outcomes – Immediate and Sustained Change in Pain

The immediate effect was measured by the pain intensity (0 – 10, 10 = worst pain) scale of the Memorial Pain Assessment Card (MPAC). (22) The sustained effect was measured by the Brief Pain Inventory (BPI), which documents pain history, intensity, location, quality and interference. Each scale for Worst Pain, Least Pain, Pain on the Average and Pain Right Now is bounded by 0 (no pain) and 10 (pain as bad as you can imagine). Scales for the extent to which pain interferes with Enjoyment of Life, Activity, Walking, Mood, Sleep, Work and Relations with Others are bounded by 0 (does not interfere) and 10 (interferes completely). (23;24) A 1.0 – 1.5 point difference on a 0 – 10 point scale was considered a clinical significant change in pain. (25;26)

Secondary Outcomes

Immediate secondary outcomes included mood, as measured by the mood (0 = 10, 10 = best mood) scale of the MPAC (22) and 60-second heart and respiratory rates. A clinically significant change in the 0 – 10 point mood scale has not been described. Sustained effects included quality of life, physical and emotional symptom distress and analgesic medication use.

Quality of life was measured using the McGill Quality of Life Questionnaire (MQOL), which consists of 17 items that are scored on a 0 – 10 scale, (0 indicates least desirable and 10 most desirable situation). The MQOL includes a total score and scores on 4 subscales: physical symptoms, psychological symptoms, existential well-being, and support. To decrease respondent burden and minimize redundancy with other measures, we omitted the physical and psychological subscales. (27;28) Effect size for the difference between “good” and “bad” days range from 1.3 to 2.2, for the difference between “bad” and “average” days from 0.6 – 1.3, and for the difference between “average” and “good” days from 0.5 to 1.0. For the purposes of this study, an effect size of 1.0 was considered a clinically significant change in quality of life. (29)

Physical and emotional symptom distress were measured using the Memorial Symptom Assessment Scale (MSAS), which evaluates the presence of and distress associated with symptoms in the prior week. Degree of physical symptom distress ranges from 0 (not present) to 4 (very much). Frequency of psychological symptoms is rated from 1 (rarely) to 4 (almost constantly). The MSAS yields a Global Distress Index, a Physical Symptom subscale score (MSAS-PHYS) and a Psychological Symptom subscale score (MSAS-PSYCH). The MSAS-PHYS was calculated as the average distress for the 12 physical symptoms (lack of energy, lack of appetite, pain, dry mouth, weight loss, feeling drowsy, shortness of breath, nausea, constipation, cough, swelling of arms or legs, difficulty swallowing). The MSAS-PSYCH was calculated as the average frequency of the 5 psychological symptoms (worrying, feeling sad, feeling nervous, feeling irritable, difficulty concentrating). The Global Distress Index was the average frequency of four psychological symptoms (worrying, feeling sad, feeling nervous,

feeling irritable) and average distress associated with six physical symptoms (lack of energy, lack of appetite, pain, dry mouth, feeling drowsy, constipation). (30-32) While the MSAS and its component scales are significantly correlated with survival, clinically significant changes have not been defined for the MSAS. (30;31;33;34)

Name, dose and frequency of symptom management medications taken over the prior 24 hours were recorded weekly to document analgesic medication use. To permit comparisons, medication doses were converted to parenteral morphine equivalents (milligrams.24 hours) using World Health Organization equianalgesic conversion ratios. (35) No data are available regarding a clinically significant change in parenteral morphine equivalents.

Adverse Events

Adverse events definitions and reporting procedures were consistent with Colorado Multiple Institutional Review Board recommendations and approved by the study Data and Safety Monitoring Board. While participants were not asked specifically about adverse events at each data collection point, standard adverse event forms were completed if a participant or hospice staff spontaneously reported an adverse event.

Statistical Analysis

Descriptive statistics and frequency distributions were generated for patient demographics, disease characteristics, prior massage, expectation of benefit and pain characteristics. Comparisons across treatment groups were carried out using t-tests for continuous and Chi-square tests for categorical variables.

Analysis of both immediate and sustained outcomes utilized a mixed-effects model (Proc Mixed procedure in SAS) that considered assessment number as a categorical factor and used an unstructured variance-covariance matrix to model the covariance structure among the repeated measures by subject. A limited set of covariates were selected prior to analysis by JK based on clinical experience and representing the domains of demographics (age and gender), general health status (comorbid conditions and Karnofsky Performance Scale), prior professional massage, expected benefit and worst pain in prior week at study entry. All covariates were included in the final models. All available data were included in the analyses. Study subjects were excluded from immediate outcome analyses if they did not participate in any treatment sessions and from sustained outcome analyses if they had no baseline or sustained outcome data available. To minimize multiple comparisons associated with repeated assessments, a summary measure was constructed for each scale from the estimated group means. For measures of sustained outcome, the primary comparison was between the average of the 3 post-baseline means and the baseline mean. For the immediate outcomes, the average across means estimated at all 6 treatment visits was used. We examined the estimates for evidence of increasing (or decreasing) trends in scores over the treatment period to verify that the choice of the summary measures was appropriate. Primary hypothesis testing was performed on MPAC Pain, BPI Worst Pain, and BPI Mean Pain. Estimates and 95% confidence intervals are presented graphically for all measures. A sensitivity analysis included a random effect to account for therapist-related clustering. The results across both analyses were consistent (parameter estimates within 10% of each other and no change in statistical significance); reported results omitted the random effect. A second sensitivity analysis examined the impact of missing data due to drop out, using a mixture model in which strata were defined as those who did or did not complete six treatments; results were consistent with reported analysis. (36)

Initial sample size calculations were based on a review of previous studies with a no treatment control group; the majority of effect sizes were within a moderate range of 0.4-0.6

S.D. (22;28;37-48) We assumed that the active control would have an effect that corresponds to 20% of this difference, thus our expected difference between the control and massage intervention would be in the range of 0.32-0.50 times the S.D. To achieve power of at least 80% to detect clinically meaningful differences, the original estimated enrollment was 440, assuming 30% loss to follow-up and a correlation of 0.5 among assessments over time. With our actual accrual, dropout rate and correlations, the power to detect small (0.2 S.D.) and medium (0.5 S.D.) effects, respectively, for the BPI average score was 0.47 and 0.97, for the BPI worst variable 0.34 and 0.87, and for the MPAC Pain scale 0.70 and 1.00. Analyses were conducted using SAS v9.1 (SAS Institute, Inc., Cary, North Carolina).

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RESULTS

Sample

Three hundred and eighty individuals (75% of those screened) were randomized. Figure 2 depicts the study flow per the Consolidated Standards of Reporting Trials (CONSORT) recommendations for randomized trials of nonpharmacologic treatment. (49;50) The enrolled/randomized group and the screened but not enrolled group were not statistically different in age, gender, race, ethnicity, marital status, payer/insurance source, highest educational level attained, location of care, cancer type, years since initial cancer diagnosis, prior experience with massage therapy, current pain intensity, least pain in the prior 24 hours, least pain in the prior week, desired pain level or pain characteristics. Those who were screened but not enrolled/randomized were more likely to have brain metastases (21% vs. 12%, $P=0.010$) and described less severe worst pain levels in the prior 24 hours and prior week (5.3 vs. 6.5, $P=0.100$ and 6.2 vs. 7.7, $P=0.002$, respectively, 0 – 10 scale).

Twenty one participants in the massage arm and 30 in the control arm did not receive any study treatments (3 massage and 8 control died; 13 massage and 16 control disenrolled; 5 massage and 6 control for varied other reasons). Seventeen in the massage arm and 15 in the control arm did not contribute any sustained outcome data (2 massage and 4 control died; 11 massage and 7 control disenrolled; 3 massage and 4 control for varied other reasons; 1 data collection packet was lost by the study site). There were no statistically significant differences between those who did and did not receive any treatments and between those who did and did not contribute sustained outcome data in age, gender, race, ethnicity, marital status, payer/insurance source, highest educational level attained, location of care, cancer type, comorbid conditions, prior experience with massage, expected helpfulness of massage, current pain intensity, or pain characteristics. Those assigned to the massage arm who did not receive any treatments had worse pain in the 24 hours prior to enrollment (7.5 vs. 6.5, $P=0.010$) compared to those who received at least 1 treatment. Those assigned to the massage arm who did not contribute any sustained outcome data had a shorter time since cancer diagnosis (1.2 vs. 2.7 years, $P=0.010$) compared to those who contributed any sustained outcome data.

Of the 188 participants allocated to massage, 172 (91%) contributed baseline data. Of these 172 massage participants, 151 (88%) were included in immediate outcome analyses. Twenty-one were excluded as they had no treatments and therefore no immediate outcome data. One

hundred and seventy-one (99%) were included in sustained outcome analyses. One was excluded due to missing baseline data.

Of the 192 participants allocated to control, 177 (92%) contributed baseline data. Of these 177 control participants, 147 (83%) were included in immediate outcome analyses. Thirty were excluded as they had no treatments and therefore no immediate outcome data. All 177 (100%) were included in sustained outcome analyses.

Participant characteristics are depicted in Table 1. There were no statistically significant baseline differences in participant characteristics, pain, quality of life or non-pain symptom distress. Routine care did not statistically differ between the study groups. There were no significant differences in number of treatments received (massage mean (SD) = 4.3 (2.4); control mean (SD) = 3.8 (2.5), $P=0.051$). Fifty-six treatment providers (23 massage (1 - 3 per site); 33 control (1 - 5 per site)) provided the study treatments.

Primary Outcomes – Immediate and Sustained Change in Pain

Both massage and simple touch were associated with statistically significant improvements in immediate and sustained pain outcomes (Table 2) Figure 3 shows both immediate (mean pre/post change (MPAC) according to treatment number and treatment group) and sustained (mean pain (BPI) according to assessment number and treatment group) pain outcomes. The immediate improvement in pain with massage, of -1.87 points (CI, -2.07, -1.67), was clinically significant. (25;26;51) While massage was statistically superior to simple touch immediately following treatment sessions (mean pain difference between study arms = -0.90 (CI, -1.19, -0.61), the difference approaches, but does not quite attain, clinical significance. Both groups demonstrated statistically, but not clinically, significant sustained improvements in pain (BPI). There were no statistically or clinically significant differences between study arms in sustained outcome pain measures. There were modest improvements, but no clinically or statistically significant differences, in leg, arm/hand, foot, gluteal, neck/back/shoulder, face/scalp, abdomen and chest pain (data not shown). Figure 4 depicts effect sizes with 95% confidence intervals by study arm, permitting comparison of massage effects across outcomes with different scale ranges.

Secondary Outcomes

Both massage and simple touch were associated with statistically significant immediate improvements in mood (Table 2). Massage was statistically superior to simple touch immediately following treatments (mean mood difference between study arms = 0.61 (CI, 0.35, 0.87)). Heart rate and respiratory rate decreased modestly in both study arms (massage: heart rate -4.20 beats per minute (CI, -4.90, -3.50); respiratory rate -1.46 breaths per minute (CI, -1.75, -1.17); control: heart rate -3.28 beats per minute (CI, -4.04, -2.57); respiratory rate -1.15 breaths per minute (CI, -1.46, -0.84)), with no clinically or statistically significant differences between study arms.

Both groups demonstrated statistically significant improvements in physical and emotional symptom distress and quality of life across weekly assessments; there were no clinically or statistically significant differences between study arms (Table 2, Figure 4). There were also no clinically or statistically significant changes in total parenteral morphine equivalents. There was no important effect modification associated with perceived helpfulness of massage therapy, presence of neuropathic pain or bony metastases.

Adverse Events

Mortality rates during the study were similar between study arms (26 (13.8%) for massage vs. 33 (17.2%) for control, $P=0.40$). Two (1.1%) serious adverse events occurred in the massage

group and 6 (3.1%) in control ($P=0.28$). Massage group adverse events included 1 respiratory infection and 1 gastrointestinal bleed. Control group adverse events included 1 fracture, 3 pain control issues, 1 seizure and 1 congestive heart failure diagnosis. One adverse event in each study group resulted in study participation discontinuation. Adverse events were infrequent, similar in both groups, and did not appear to be related to treatments.

DISCUSSION

Massage appeared to have immediately beneficial effects on pain and mood among patients with advanced cancer. Both the massage and simple touch groups had statistically, although not clinically, significant improvements in pain and quality of life over time despite no increases in total analgesic medication use. While there is no definition of clinically significant change in symptom distress as measured by the MSAS, the observed improvements were minimal. Dispelling common concerns about safety of massage in cancer, there were no significant differences in adverse events or mortality among this advanced cancer population. This study provides a promising model for future clinical trials in the hospice/palliative care population, demonstrating feasibility of the hospice-based research network as a venue for conducting randomized trials.

That both the massage and simple touch groups experienced statistically, although not clinically, significant improvements in pain, quality of life, and physical and emotional symptom distress over time without increasing analgesic medication use is an interesting finding, especially given study participants' advanced disease status. Several studies have demonstrated relatively preserved quality of life and stable symptom distress among hospice/palliative care populations. None of these studies documented analgesic medication use, so it is unclear whether the stable quality of life and symptoms in prior studies was due to aggressive symptom management consistent with excellent hospice/palliative care. The observed relative stability of these outcomes in our study may thus be due to massage, effects of simple touch, or other beneficial aspects of hospice/palliative care. (4;27;52;53)

Previous research has supported the value of massage for relieving pain in cancer patients, although study limitations (small sample size, lack of adequate control groups) and conflicting results make firm conclusions impossible. (54-56) While some massage studies have demonstrated improvements in pain, nausea and other symptoms (57-60), others have not. (11;61;62) The most consistent effect of massage has been reduction of subjective levels of anxiety, which may be more sensitive than objective indicators of relaxation/arousal. (56;63) Given that there are so few published randomized trials of massage therapy, particularly in this population, there are few available direct comparisons.

The REST study suggests an immediate beneficial effects of massage for pain and mood in advanced cancer; however, it is not clear if these benefits endured for hours or several days. This question is important for future research. A small sample of patients who were interviewed after study completion indicated that massage offered respite or sanctuary, providing comfort and relaxation, a time for reflection and a sense of connection to another. Several qualitative studies corroborate this value of massage for promoting relaxation and feelings of well-being. (60;64;65)

The strengths of the REST study design enhance its contributions to the evidence base, particularly incorporation of randomized assignment to a control group that was specifically designed to control for time, attention, touch and healing intent, its relatively large sample size and multisite nature. (17) The study has good external validity, in that the massage therapists were encouraged to use their own clinical judgment in designing the treatment within the

parameters of time and type of stroke used; however, many therapists do incorporate music and essential oils into their usual practice.

The study does have limitations. First, measurement or reporting bias is possible, as most measures were by self report and immediate outcome measures were obtained by treating therapists, who were not blinded to treatment assignment. This issue was addressed by using previously developed scales with established reliability, validity and sensitivity to change as well as pilot testing the instruments. Second, participants may not be representative of all advanced cancer patients. By design, this study included only English-speaking adults with an estimated life expectancy of 3 weeks or greater who were able to participate. Individuals with advanced cancer who participated in this study may be systematically different from those who were not approached for study participation or those who did not meet study eligibility criteria. Five hundred and nine patients were screened for study enrollment, representing a small proportion of potentially available patients but a common experience in hospice and palliative care-based research. (12;66;67) There is no theoretical reason to believe that massage effectiveness would differ between these groups. In addition, given that it is impossible to completely blind patients to massage, those who volunteer for a massage study may have a higher expectancy of benefit than those who do not. This potential bias was addressed by referring to the intervention and control conditions as “moving touch” and “non-moving touch” throughout the trial. Also, there was no association between expected helpfulness of massage and study outcomes. Third, given the nature of this population, we expected a significant drop-out rate due to death or disability. We attempted to lessen the impact of potential incomplete follow up through eligibility criteria, sample size calculation and analytic approach, assuming that we would experience 30% loss to follow up. In actual experience, 37 massage and 45 control subjects did not receive any study treatments ($n=82$, or 21.6%). Seventeen massage and 15 control subjects did not contribute any sustained outcomes data ($n=32$, or 8.4%). While there were few differences between those who did and did not receive treatments or did and did not contribute sustained outcome data, it is possible that there were unmeasured systematic differences that would affect study outcomes. Fourth, the study lacked a “usual care” control arm. The control condition, which was designed as an inactive control exposure, appears to have had a beneficial effect over time similar to that of massage. However, without a usual care control arm the differential beneficial effect is not conclusive. Conducting a 3-arm trial, comparing massage to a control exposure and to usual care would be ideal, but was not feasible due to required sample size and consequent required budget. Fifth, the lack of published clinically significant differences for the MPAC mood scale and the MSAS make interpretation of statistically significant findings difficult. If the same clinically significant difference criteria for the MPAC pain scale (difference of 1.0 – 1.5 points) are applied to the MPAC mood findings, then the immediate improvement of 1.58 points following massage would be considered clinically significant. However, the mean difference between the massage and control arms (0.61) would not reach the level of clinical significance. For the MSAS, the observed improvements, while statistically significant, are quite small (0.07 – 0.16) and likely have little clinical significance.

This multisite randomized clinical trial, which was conducted primarily in hospice, suggests that massage may be more effective than simple touch in decreasing pain and improving mood immediately following treatment sessions. Sustained benefits of massage in this population are less evident. Patients with advanced cancer may be touch-deprived, due to social isolation or fear of causing harm. These findings support offering massage for immediate symptom relief and considering the potential therapeutic benefits of simple touch, as could be provided by family members or hospice volunteers, as an adjunct to usual care. Furthermore, the REST study provides a model for future clinical trials examining the efficacy of therapies with potential to mediate the multiple distressing symptoms encountered in advanced illness.

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Figure 1.
Study Overview: Timing of Study Procedures.

Figure 2. Study Flow Diagram

“Assessments” refer to the weekly or sustained outcomes. Immediate outcome data collection occurred in conjunction with every treatment session. IQR = interquartile range; max = maximum; min = minimum.

Figure 3. Immediate and Sustained Pain Outcomes

Panel A. Immediate Outcomes: Mean Pain Pre/Post Change (MPAC) According to Treatment Number and Treatment Group (squares for Massage Therapy and circles for Control). Pre and post treatment pain for immediate outcomes were measured with the Memorial Pain Assessment Card (0 – 10 scale, 10 = worst pain). Mean pain changes for immediate outcomes represent the mean of the post-pre assessments at each treatment visit. Estimates and 95% confidence intervals were obtained from a mixed effects model adjusted for age, comorbid conditions, gender, prior professional massage, worst pain in prior week at study entry, and Karnofsky Performance Scale. The number of participants with treatments at each visit is noted above the x-axis. MPAC = Memorial Pain Assessment Card; CI = Confidence Interval. **Panel B. Sustained Outcomes: Mean Pain (BPI) According to Assessment Number and Treatment Group (squares for Massage Therapy and circles for Control).** Sustained outcome pain was measured with the Brief Pain Inventory (0 – 10 scale, 10 = worst pain). Mean pain estimates and 95% confidence intervals at each sustained assessment visit were obtained from a mixed effects model adjusted for age, comorbid conditions, gender, prior professional massage, worst pain in prior week at study entry, and Karnofsky Performance Scale. The number of participants with sustained assessments at each visit is noted above the x-axis. BPI = Brief Pain Inventory; CI = Confidence Interval.

Figure 4. Immediate and Sustained Effects

Effect sizes with 95% confidence intervals and p-values shown for study outcomes according to Massage Therapy (squares) and Control (circles) arms. Data represent improvement if >0 and worsening if <0. Effect sizes adjusted for age, comorbid conditions, gender, prior professional massage, worst pain in prior week at study entry, and functional status (Karnofsky Performance Scale). Asterisks denote primary study outcomes. MPAC = Memorial Pain Assessment Card; BPI = Brief Pain Inventory; MSAS = Memorial Symptom Assessment Scale; MQOL = McGill Quality of Life Questionnaire.

Table 1

Participant Characteristics (n=380)

	Massage Therapy (n=188)	Control (n=192)
Gender (female), n (%)	120 (64)	112 (58)
Age, years, mean (SD)	65.2 (14.4)	64.2 (14.4)
Race, Non-Hispanic White, n (%)	161 (86)	164 (85)
Married or committed relationship, n (%)	93 (49)	77 (40)
Primary payer/insurance, Medicare, n (%)	114 (61)	109 (57)
Education, college or higher, n (%)	72 (39)	79 (42)
Location of care, home, n (%)	145 (77)	155 (81)
Years following initial cancer diagnosis, mean (SD)	2.5 (3.9)	2.9 (5.1)
Cancer type (5 most common diagnoses), n (%)		
Lung	48 (26)	48 (25)
Breast	34 (18)	29 (15)
Pancreas	13 (7)	22 (12)
Colorectal	12 (6)	17 (9)
Prostate	10 (5)	11 (6)
Presence of any metastases, n (%)	188 (100)	192 (100)
Presence of bony metastases, n (%)	55 (29)	46 (24)
Number of comorbid conditions, mean (SD)	2.2 (2.2)	2.3 (2.2)
Concomitant medical conditions*, n (%)		
Medical diagnoses	104 (55)	110 (57)
Neurologic diagnoses	13 (7)	18 (9)
Vascular diagnoses	18 (10)	13 (7)
Received prior professional massage therapy, n (%)	76 (40)	74 (39)
Perceived helpfulness of massage therapy [†] , mean (SD)	4.0 (1.0)	3.9 (1.1)
Worst pain prior 24 hours (0 – 10 scale), mean (SD)	6.7 (2.4)	6.4 (2.5)
Worst pain prior week (0 – 10 scale), mean (SD)	8.0 (1.9)	7.6 (2.2)
Goal pain level (0 – 10 scale), mean (SD)	0.2 (0.8)	0.3 (0.8)
Constant pain present, n (%)	97 (52)	103 (55)
Intermittent pain present, n (%)	133 (71)	135 (70)
Brief pain present, n (%)	56 (30)	46 (24)
Neuropathic pain present [‡] , n (%)	38 (23)	51 (29)
Number of body sections with pain, mean (SD)	6.9 (6.5)	7.4 (6.5)
Routine care, median [IQR]		
Chaplain	0 [0, 15]	0 [0, 15]
Home Health Aid	0 [0, 45]	0 [0, 51.3]
Nurse	45 [22.5, 90]	48.8 [22.5, 103.8]
Physician	0 [0, 8.75]	0 [0, 3.8]
Social Worker	15 [0, 26.3]	15 [0, 31.3]
Volunteer	0 [0, 7.5]	0 [0, 7.5]

* "Medical diagnoses" = heart disease, diabetes, HIV/AIDS, hypertension, infection, kidney/renal disease, liver disease, lung disease, pulmonary embolus;

"Neurologic diagnoses" = delirium, dementia, neurologic disease (e.g. Parkinson's, amyotrophic lateral sclerosis, multiple sclerosis, etc.), stroke; "Vascular diagnoses" = deep venous thrombosis, peripheral vascular disease, pressure ulcers

[†] Perceived helpfulness of massage therapy for pain, 1 – 5 scale, 1=not at all helpful, 5=very helpful

[‡] Presence of neuropathic pain defined as score of 3 or higher on the composite Neuropathic Pain Scale

Table 2

Summary of Immediate and Sustained Effects, Massage Therapy and Control

Instrument	Massage Therapy			Control	Massage Therapy vs Control	
	Range	Mean Baseline	Mean Change		95% CI Mean Change	Mean Difference
Immediate Effects						
Mood (MPAC)	0-10 (10=best)	6.5 (2.1)	1.58	(1.40, 1.76)	0.97	0.61
Pain (MPAC) *	0-10 (10=worst)	3.7 (2.6)	-1.87	(-2.07, -1.67)	-0.97	-0.90
Heart Rate	NA	76.4 (13.3)	-4.20	(-4.9, -3.50)	-3.28	-0.92
Respiratory Rate	NA	17.1 (5.0)	-1.46	(-1.75, -1.17)	-1.15	-0.31
Sustained Effects						
Mean Pain (BPI) *	0-10 (10=worst)	4.6 (1.6)	-0.33	(-0.54, -0.12)	-0.40	0.07
Worst Pain (BPI) *	0-10 (10=worst)	8.0 (1.9)	-0.74	(-1.05, -0.43)	-0.60	-0.14
Pain Interference (BPI)	0-10 (10=worst)	4.5 (2.6)	-0.33	(-0.61, -0.05)	-0.43	0.11
Global Distress Index (MSAS)	0-10 (10=best)	2.7 (0.6)	-0.11	(-0.19, -0.03)	-0.11	-0.002
Physical Symptoms (MSAS)	0-10 (10=best)	2.7 (0.6)	-0.10	(-0.18, -0.02)	-0.07	-0.03
Psychological Symptoms (MSAS)	0-10 (10=best)	2.6 (0.8)	-0.09	(-0.22, 0.04)	-0.16	0.06
Overall Quality of Life (MQOL)	0-10 (10=best)	6.2 (2.5)	0.36	(0.04, 0.68)	0.29	0.08
Physical Well-Being (MQOL)	1-4 (4=worst)	5.3 (2.6)	0.26	(-0.11, 0.63)	0.44	-0.18
Existential (MQOL)	1-4 (4=worst)	7.5 (1.7)	-0.01	(-0.22, 0.20)	0.08	-0.09
Support (MQOL)	1-4 (4=worst)	8.8 (1.7)	-0.17	(-0.39, 0.05)	-0.02	-0.14
Parenteral Morphine Equivalents [†]	NA	34.2 (15.3- 83.3)	0.007	(-0.09, 0.77)	0.11	-0.10

Mean scores with Standard Deviations and 95% confidence intervals (CI) shown for immediate and sustained primary and secondary study outcomes. Abbreviations: Memorial Pain Assessment Card (MPAC); Brief Pain Inventory (BPI); Condensed Memorial Symptom Assessment Scale (MSAS); McGill Quality of Life Questionnaire (MQOL).

* Primary outcomes.

[†]Median (25-75 percentiles). Comparisons adjusted for age, comorbid conditions, gender, prior professional massage, worst pain in prior week at study entry, and Karnofsky Performance Scale. For the immediate outcomes mixed effects models, there were 151 massage and 147 controls. For the sustained outcomes mixed effects models, there were 171 massage and 177 controls. Mean changes for immediate outcomes represent the mean of the post-pre assessments for all five treatments versus the mean post-pre assessment from the baseline, and the mean changes for the sustained outcomes represent the difference between the average of the three post-baseline assessments and the baseline mean.