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Massage Therapy versus Simple Touch to Improve Pain and Mood in Patients with Advanced Cancer

A Randomized Trial

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

Objective: To evaluate the efficacy of massage for decreasing pain and symptom distress and improving quality of life among persons with advanced cancer.

Design: Multisite, randomized clinical trial.

Setting: Population-based Palliative Care Research Network.

Patients: 380 adults with advanced cancer who were experiencing moderate-to-severe pain; 90% were enrolled in hospice.

Intervention: Six 30-minute massage or simple-touch sessions over 2 weeks.

Measurements: Primary outcomes were immediate (Memorial Pain Assessment Card, 0- to 10-point scale) and sustained (Brief Pain Inventory [BPI], 0- to 10-point scale) change in pain. Secondary outcomes were immediate change in mood (Memorial Pain Assessment Card) and 60-second heart and respiratory rates and sustained change in quality of life (McGill Quality of Life Questionnaire, 0- to 10-point scale), symptom distress (Memorial Symptom Assessment Scale, 0- to 4-point scale), and analgesic medication use (parenteral morphine equivalents [mg/d]). Immediate outcomes were obtained just before and after each treatment session. Sustained outcomes were obtained at baseline and weekly for 3 weeks.

Results: 298 persons were included in the immediate outcome analysis and 348 in the sustained outcome analysis. A total of 82 persons did not receive any allocated study treatments (37 massage patients, 45 control participants). Both groups demonstrated immediate improvement in pain (massage, −1.87 points [95% CI, −2.07 to −1.67 points]; control, −0.97 point [CI, −1.18 to −0.76 points]) and mood (massage, 1.58 points [CI, 1.40 to 1.76 points]; control, 0.97 point [CI, 0.78 to 1.16 points]). Massage was superior for both immediate pain and mood (mean difference, 0.90 and 0.61 points, respectively; $P < 0.001$). No between-group mean differences occurred over time in sustained pain (BPI mean pain, 0.07 point [CI, −0.23 to 0.37 points]; BPI worst pain, −0.14 point [CI, −0.59 to 0.31 points]), quality of life (McGill Quality of Life Questionnaire overall, 0.08 point [CI, −0.37 to 0.53 points]), symptom distress (Memorial Symptom Assessment Scale global distress index, −0.002 point [CI, −0.12 to 0.12 points]), or analgesic medication use (parenteral morphine equivalents, −0.10 mg/d [CI, −0.25 to 0.05 mg/d]).

Limitations: The immediate outcome measures were obtained by unblinded study therapists, possibly leading to reporting bias and the overestimation of a beneficial effect. The generalizability to all patients with advanced cancer is uncertain. The differential beneficial effect of massage therapy over simple touch is not conclusive without a usual care control group.

Conclusion: 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 groups, the potential benefits of attention and simple touch should also be considered in this patient population.

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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 the efficacy of therapies that may mediate these symptoms deserve the highest priority. The Institute of Medicine and the National Institutes of Health recommend research directed at improving end-of-life care (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 the therapist's intention (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 the use and growing acceptance of massage therapy, few randomized clinical trials have assessed its efficacy. Large trials have been difficult to design and carry out; challenges include frailty of patients with late-stage cancer and reluctance of health care providers to refer patients because of the possibility of randomization to non–massage therapy control (12).

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Summary for Patients I-38

Web-Only

Appendix

Appendix Figure

Conversion of graphics into slides

Context

Some patients nearing death seek pain relief with massage, but little is known about the effectiveness of massage in managing pain in palliative care settings.

Contribution

In this randomized trial in 380 patients with advanced cancer, improvement in pain and mood immediately after treatment was greater with massage than with simple touch. Unfortunately, there were no sustained differences in pain, quality of life, or analgesic use during 3 weeks. Adverse effects were infrequent and similar in both groups.

Implication

Massage may offer some immediate relief for patients with advanced cancer, but the absence of sustained effects demonstrates the need for more effective strategies to manage pain at the end of life.

—The Editors

Therapeutic massage can reduce pain and improve symptom distress and quality of life for patients with cancer at the end of life. The purpose of the REST (Reducing End-of-Life Symptoms with Touch) study was to evaluate the efficacy of massage compared with 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

We conducted this prospective, 2-group, randomized, single-blind trial between November 2003 and October 2006. After we evaluated patients for inclusion and exclusion criteria, patients provided written informed consent. Then we randomly assigned patients to a treatment group (massage) or control exposure (simple touch). **Figure 1** depicts the timing of the study procedures for a hypothetical participant. We collected individual characteristics, disease, pain characteristics, symptom distress, quality of life, functional status (Karnofsky Performance Scale score) (13), expected helpfulness of massage for pain, and concurrent interventions (pharmacologic and nonpharmacologic) at baseline (within 72 hours of study enrollment) and at 3 subsequent weekly visits over the 3 to 4 weeks of participation (sustained outcomes). Final data collection occurred approximately 1 week after the final treatment. Data collectors were blinded to treatment assignment. Participants received up to six 30-minute treatments over 2 weeks, with at least 24 hours between treatment sessions. The initial treatment session occurred within 48 hours of baseline data collection. The treatment provider and patient determined the scheduling of treatment sessions. Treatment providers who were not blinded to treatment assignment obtained the immediate outcomes just before and after every treatment session. 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.

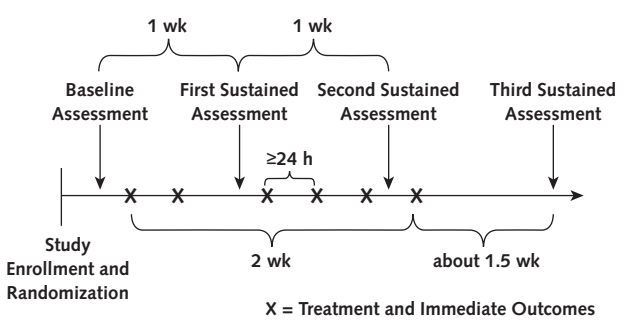
Setting and Participants

Study sites included 15 U.S. hospices that are members of the Population-based Palliative Care Research Network (PoPCRN) (14) and the University of Colorado Cancer Center, Aurora, Colorado. 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 (score ≥4 on a 0- to 10-point scale) in the week before enrollment, an anticipated life expectancy of at least 3 weeks, and the ability to consent. Exclusion criteria included receipt of professional massage within 1 month of enrollment, anticoagulant therapy, known platelet count less than 10×10^9 cells/L, 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. Two designated investigators randomly assigned patients; assignments were transmitted back to the requesting site. All study personnel other than the on-site study coordinators and these 2 designated investigators were blinded to the randomization sequence. An SAS software program (SAS Institute, Cary, North Carolina) generated the randomization sequence by producing a randomized block design stratified by study site. Block size randomly varied among 2, 4, and 6 so that it was not possible to predict the next assignment. To minimize the likelihood that potential participants would decline enrollment because of reluctance to be randomly assigned, we offered massage after study completion to those assigned to the control group.

Figure 1. **Study overview: timing of study procedures.**



Experimental Treatment: Massage Therapy

The massage intervention included gentle effleurage, petrissage, and myofascial trigger point release. Effleurage is a smooth, gliding stroke; petrissage is squeezing, rolling, and kneading the muscles; and 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 frequency of rhythm, rate, or stroke; sequence or mix of strokes; time spent in each stroke; stroke length; and body area massaged (16). Massage 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. Therapists appropriately modified massage in persons with skin fragility, postural limitations, edema, osteoporosis, or bone metastasis. Therapists avoided sites of inflammation or infection, hyperesthesias, injury, surgery, ports, catheters, deep venous thrombosis, and tumors. Therapists identified and treated up to 3 myofascial trigger points per session (located 15% to 25% of the time in the neck, upper trapezius, and lower trapezius regions). One 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. Fewer than 25% of participants were unclothed during treatments. Massage was performed by licensed massage therapists who had at least 6 months of experience treating patients with 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.

Control Exposure

We designed the control exposure, simple touch, 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 backward from 100 by 7, reciting nursery rhymes, or planning their day's activities (18, 19). The control treatments were provided by individuals with no past 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. We monitored adherence to study protocols during twice-yearly site visits. Treatment providers in both groups used Biotone hypoallergenic unscented massage cream (Biotone, San Diego, California). For the purposes of standardization and to mediate the presence of intervening variables, we did not permit music, essential oils, or energy work and instructed treatment providers to limit their communication to providing instructions or responding to therapy-related questions. To minimize variation by treatment provider, 1 primary massage therapist or simple-touch provider per participant at each study site administered study treatments.

Outcomes and Follow-up

We used face-to-face, interviewer-administered questionnaires to collect all study data.

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

Primary Outcomes: Immediate and Sustained Change in Pain

The immediate effect was measured by the pain intensity scale of the Memorial Pain Assessment Card (MPAC) (0 to 10 points; 10 = worst pain) (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, average pain, and current pain is bounded by 0 (no pain) and 10 (worst pain 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- to 1.5-point difference on the scale was considered to be a clinically significant change in pain (25, 26).

Secondary Outcomes

Immediate secondary outcomes included mood, measured by the MPAC mood scale (0 to 10 points; 10 = best mood) (22) and by 60-second heart and respiratory rates. A clinically significant change in the 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 by using the McGill Quality of Life Questionnaire, which consists of 17 items (0- to 10-point scale; 0 indicates least desirable and 10 indicates most desirable situation). The questionnaire 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 sizes for the difference between "good" and "bad" days range from 1.3 to 2.2; those for the difference between "bad" and "aver-

age" days range from 0.6 to 1.3; and those for the difference between "average" and "good" days range from 0.5 to 1.0. For the purposes of this study, we considered an effect size of 1.0 to be a clinically significant change in quality of life (29).

We measured physical and emotional symptom distress by using the Memorial Symptom Assessment Scale (MSAS), which evaluates the presence of and distress associated with symptoms in the past week. Degree of physical symptom distress ranges from 0 (not present) to 4 (very much present). The MSAS rates frequency of psychological symptoms from 1 (rarely) to 4 (almost constantly). The MSAS yields a global distress index, a physical symptom subscale score, and a psychological symptom subscale score. The physical symptom subscale score was calculated as the average distress for the 12 physical symptoms (lack of energy, lack of appetite, pain, dry mouth, weight loss, drowsiness, shortness of breath, nausea, constipation, cough, swelling of arms or legs, and difficulty swallowing) and as the average frequency of the 5 psychological symptoms (worry, sadness, nervousness, irritability, and difficulty concentrating). The global distress index was the average frequency of 4 psychological symptoms (worry, sadness, nervousness, and irritability) and average distress associated with 6 physical symptoms (lack of energy, lack of appetite, pain, dry mouth, drowsiness, and constipation) (30–32). Although the MSAS and its component scales are statistically significantly correlated with survival, clinically significant changes have not been defined (30, 31, 33, 34).

We recorded the name, dose, and frequency of symptom management medications taken during the past 24 hours every week to document analgesic medication use. To permit comparisons, we converted medication doses to parenteral morphine equivalents (mg/d) by using World Health Organization equianalgesic conversion ratios (35). No data are available regarding a clinically significant change in parenteral morphine equivalents.

Adverse Events

Adverse event definitions and reporting procedures were consistent with Colorado Multiple Institutional Review Board recommendations and were approved by the study's data and safety monitoring board. Although we did not specifically ask participants about adverse events at each data collection point, we completed standard adverse event forms if a participant or hospice staff spontaneously reported an adverse event.

Statistical Analysis

We generated descriptive statistics and frequency distributions for patient demographic characteristics, disease characteristics, experience with massage therapy, expectation of benefit, and pain characteristics. We made comparisons across treatment groups by using *t* tests for continuous and chi-square tests for categorical variables.

We analyzed both immediate and sustained outcomes by using a mixed-effects model (PROC MIXED procedure in SAS software program) 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 participant. We selected a limited set of covariates before analysis on the basis of clinical experience that represented the domains of demographic characteristics (age and sex), general health status (comorbid conditions and Karnofsky Performance Scale score), experience with massage therapy, expected benefit, and worst pain in past week at study entry. We included all covariates in the final models and all available data in the analyses. We excluded study participants 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, we constructed a summary measure for each scale from the estimated group means. For measures of sustained outcome, the primary comparison was between the average of the 3 postbaseline means and the baseline mean. For the immediate outcomes, we used the average across means estimated at all 6 treatment visits. 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. We performed primary hypothesis testing on MPAC pain, BPI worst pain, and BPI mean pain. We present estimates and 95% CIs 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 effect of missing data due to withdrawals by using a mixture model in which strata were defined as participants who did or did not complete 6 treatments; results were consistent with reported analysis (36).

We based initial sample size calculations on a review of previous studies with a no-treatment control group; most effect sizes were within a moderate range of 0.4 to 0.6 SD (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 to 0.50 times the SD. To achieve power of at least 80% to detect clinically meaningful differences, we estimated enrollment at 440, assuming 30% loss to follow-up and a correlation of 0.5 among assessments over time. With our actual accrual, withdrawal rate, and correlations, the power to detect small (0.2 SD) and medium (0.5 SD) effects were 0.47 and 0.97, respectively, for the BPI average score; 0.34 and 0.87, respectively, for BPI worst pain; and 0.70 and 1.00, respectively, for MPAC pain. We conducted analyses by using SAS software, version 9.1.

Role of the Funding Source

The study was funded by the National Center for Complementary and Alternative Medicine, Mendel/

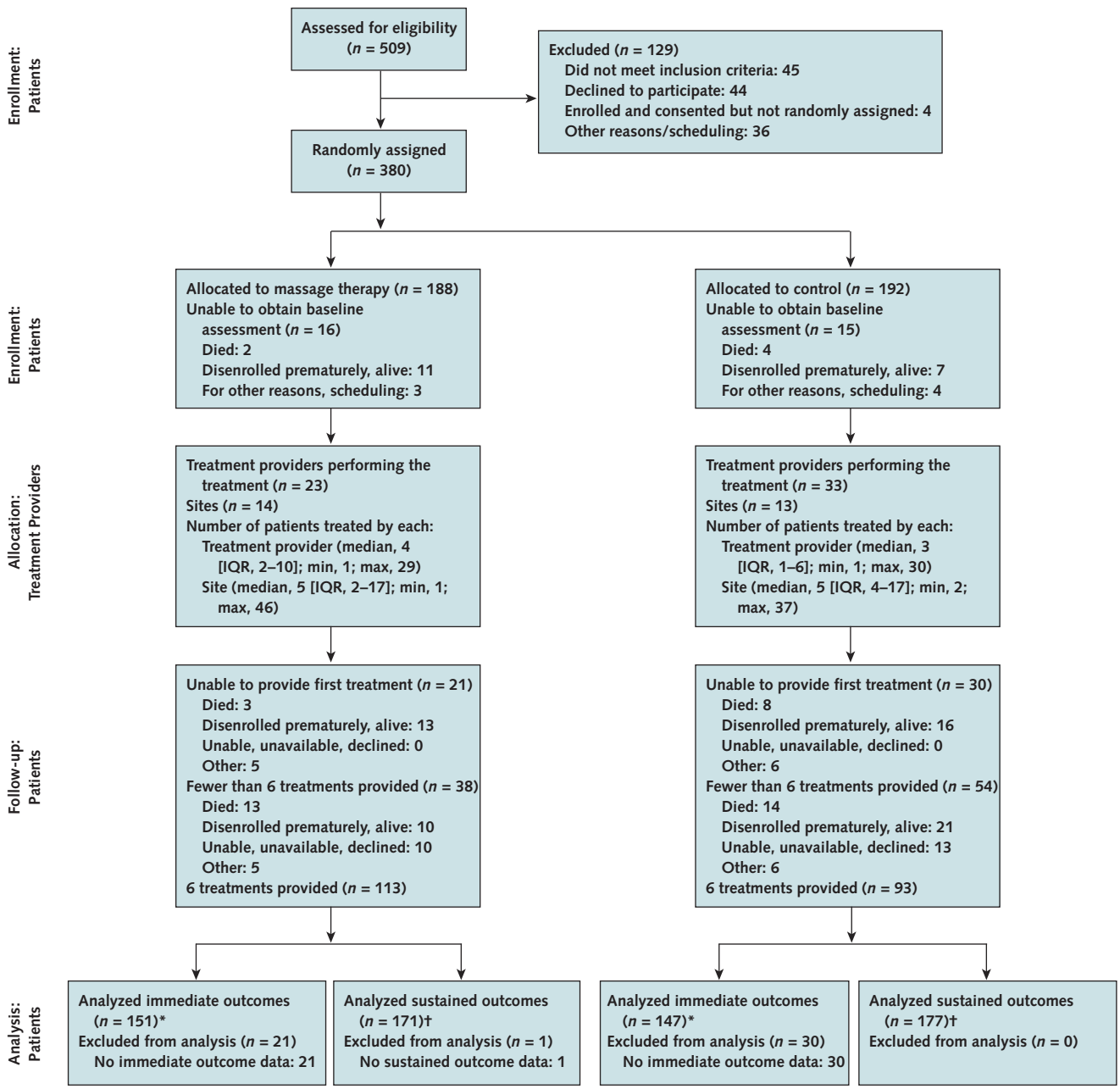
Asarch Lung Cancer Family Foundation Grants Program, Paul Beeson Physician Faculty Scholars in Aging Research Award, and Robert Wood Johnson Generalist Physician Faculty Scholars Program. The funding sources had no role in study conceptualization, design, implementation, analysis, interpretation, or manuscript preparation.

RESULTS

Sample

We randomly assigned 380 individuals (75% of those screened) to one of the 2 groups. **Figure 2** depicts the study flow per the Consolidated Standards of Reporting Trials (CONSORT) recommendations for randomized trials of

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.

* Number who had any treatment: 113 + 38 for massage therapy and 93 + 54 for control.

† Number with baseline or any sustained outcome assessments: 188 − 17 for massage therapy and 192 − 15 for control.

Table 1. **Participant Characteristics***

Characteristic	Massage Therapy Group (*n* = 188)	Control Group (*n* = 192)
Women, *n (%)*	120 (64)	112 (58)
Mean age (SD), *y*	65.2 (14.4)	64.2 (14.4)
Non-Hispanic white race, *n (%)*	161 (86)	164 (85)
Married or in a committed relationship, *n (%)*	93 (49)	77 (40)
Medicare as primary payer/insurance, *n (%)*	114 (61)	109 (57)
College-level or higher education, *n (%)*	72 (39)	79 (42)
Receiving care at home, *n (%)*	145 (77)	155 (81)
Mean time after initial cancer diagnosis (SD), *y*	2.5 (3.9)	2.9 (5.1)
Cancer type, *n (%)*		
Lung	48 (26)	48 (25)
Breast	34 (18)	29 (15)
Pancreatic	13 (7)	22 (12)
Colorectal	12 (6)	17 (9)
Prostate	10 (5)	11 (6)
Presence of metastasis, *n (%)*	188 (100)	192 (100)
Presence of bone metastasis, *n (%)*	55 (29)	46 (24)
Mean number of comorbid conditions (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 previous professional massage therapy, *n (%)*	76 (40)	74 (39)
Mean perception of helpfulness of massage therapy (SD)‡	4.0 (1.0)	3.9 (1.1)
Mean score of worst pain in past 24 hours (SD) (scale, 0–10 points)	6.7 (2.4)	6.4 (2.5)
Mean score of worst pain in past week (SD) (scale, 0–10 points)	8.0 (1.9)	7.6 (2.2)
Mean goal pain level (SD) (scale, 0–10 points)	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)
Mean number of body sections with pain (SD)	6.9 (6.5)	7.4 (6.5)
Median frequency of routine care (IQR), *h/wk*		
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)

IQR = interquartile range.
* Of 380 participants.
† "Medical diagnoses" are heart disease, diabetes, HIV/AIDS, hypertension, infection, kidney or renal disease, liver disease, lung disease, or pulmonary embolus. "Neurologic diagnoses" are delirium, dementia, neurologic disease (for example, Parkinson disease, amyotrophic lateral sclerosis, or multiple sclerosis) or stroke. "Vascular diagnoses" are deep venous thrombosis, peripheral vascular disease, and pressure ulcers.
‡ Perceived helpfulness of massage therapy for pain was measured on a 1- to 5-point scale, in which 1 means "not at all helpful" and 5 means "very helpful."
§ Presence of neuropathic pain was defined as score ≥3 on the composite Neuropathic Pain Scale.

nonpharmacologic treatment (49, 50). The enrolled and randomized group and the screened but not enrolled group did not differ in age, sex, race or ethnicity, marital status, payer or insurance source, highest educational level attained, location of care, cancer type, years since initial cancer diagnosis, experience with massage therapy, current pain intensity, least pain in the past 24 hours, least pain in the past week, desired pain level, or pain characteristics. Those who were screened but not enrolled were more likely to have brain metastases (21% vs. 12%; $P = 0.010$) and described less severe levels of worst pain in the past 24 hours and past week (0- to 10-point scale, 5.3 vs. 6.5 points [$P = 0.100$] and 6.2 vs. 7.7 points [$P = 0.002$], respectively).

Twenty-one participants in the massage group and 30 in the control group did not receive any study treatments (3 massage patients and 8 control participants died; 13 massage patients and 16 control participants withdrew; 5 massage patients and 6 control participants for other reasons). Seventeen patients in the massage group and 15 in the control group did not contribute any sustained outcome data (2 massage patients and 4 control participants died; 11 massage patients and 7 control participants withdrew; 3 massage patients and 4 control participants for other reasons; 1 data collection packet was lost by the study site). Age, sex, race or ethnicity, marital status, payer or insurance source, highest educational level attained, location of care, cancer type, comorbid conditions, experience with massage therapy, expected helpfulness of massage, current pain intensity, or pain characteristics did not statistically significantly differ between patients who did and those who did not receive any treatments and between

patients who did and those who did not contribute sustained outcome data. Participants assigned to the massage group who did not receive any treatments had worse pain in the 24 hours before enrollment than did those who received at least 1 treatment (0- to 10-point scale, 7.5 vs. 6.5 points; $P = 0.010$). Those assigned to the massage group who did not contribute any sustained outcome data had a shorter time since cancer diagnosis than did those who contributed any sustained outcome data (1.2 years vs. 2.7 years; $P = 0.010$).

Table 1 lists participant characteristics. Baseline participant characteristics, pain, quality of life, or nonpain symptom distress and routine care did not statistically significantly differ between the study groups. The mean number of treatment sessions received also did not statistically significant differ (massage group, 4.3 treatment sessions [SD, 2.4]; control group, 3.8 treatment sessions [SD, 2.5]; $P = 0.051$). Fifty-six treatment providers (23 massage [1 to 3 per site] and 33 control [1 to 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 before and after 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 (−1.87 points [95% CI, −2.07 to −1.67 points]) was clinically significant (25, 26, 51). Although massage was statistically superior to simple touch immediately after treatment sessions (mean pain difference between study groups, −0.90 point [CI, −1.19 to −0.61 points]), the difference approaches but does not attain clinical significance. Both groups demonstrated statistically, but not clinically, significant sustained improvements in pain (BPI). No statistically or clinically significant differences between study groups occurred in sustained outcome pain measures. Leg; arm and hand; foot; gluteal; neck, back, and shoulder; face and scalp; abdomen; and chest pain modestly—but not clinically or statistically significantly—improved (data not shown). The **Appendix Figure** (available at www.annals.org) depicts effect sizes with 95% CIs by study group, permitting comparison of massage effects across outcomes with different scale ranges.

Table 2. **Summary of Immediate and Sustained Effects of Massage Therapy and Control***

Variable	Massage Therapy Group			Control Group		Mean Difference (95% CI): Massage Therapy Group vs. Control Group
	Scale Range	Mean Baseline Value (SD)	Mean Change (95% CI)	Mean Baseline Value (SD)	Mean Change (95% CI)	
Immediate effects						
Mood (MPAC)	0–10 (10 = best)	6.5 (2.1)	1.58 (1.40 to 1.76)	6.5 (2.3)	0.97 (0.78 to 1.16)	0.61 (0.35 to 0.87)
Pain (MPAC)†	0–10 (10 = worst)	3.7 (2.6)	−1.87 (−2.07 to −1.67)	3.4 (2.5)	−0.97 (−1.18 to −0.76)	−0.90 (−1.19 to −0.61)
Heart rate, *beats/min*	NA	76.4 (13.3)	−4.20 (−4.9 to −3.50)	76.4 (13.3)	−3.28 (−4.04 to −2.57)	−0.92 (−1.94 to 0.10)
Respiratory rate, *breaths/min*	NA	17.1 (5.0)	−1.46 (−1.75 to −1.17)	17.1 (5.0)	−1.15 (−1.46 to −0.84)	−0.31 (−0.74 to 0.12)
Sustained effects						
Mean pain (BPI)†	0–10 (10 = worst)	4.6 (1.6)	−0.33 (−0.54 to −0.12)	4.5 (1.8)	−0.40 (−0.62 to −0.18)	0.07 (−0.23 to 0.37)
Worst pain (BPI)†	0–10 (10 = worst)	8.0 (1.9)	−0.74 (−1.05 to −0.43)	7.6 (2.2)	−0.60 (−0.92 to −0.28)	−0.14 (−0.59 to 0.31)
Pain interference (BPI)	0–10 (10 = worst)	4.5 (2.6)	−0.33 (−0.61 to −0.05)	4.6 (2.3)	−0.43 (−0.72 to −0.14)	0.11 (−0.29 to 0.51)
Global distress index (MSAS)	0–10 (10 = best)	2.7 (0.6)	−0.11 (−0.19 to −0.03)	2.7 (0.6)	−0.11 (−0.20 to −0.02)	−0.002 (−0.12 to 0.12)
Physical symptoms (MSAS)	0–10 (10 = best)	2.7 (0.6)	−0.10 (−0.18 to −0.02)	2.6 (0.6)	−0.07 (−0.15 to 0.008)	−0.03 (−0.14 to 0.08)
Psychological symptoms (MSAS)	0–10 (10 = best)	2.6 (0.8)	−0.09 (−0.22 to 0.04)	2.6 (0.8)	−0.16 (−0.29 to −0.02)	0.06 (−0.13 to 0.25)
Overall quality of life (MQOL)	0–10 (10 = best)	6.2 (2.5)	0.36 (0.04 to 0.68)	6.3 (2.4)	0.29 (−0.03 to 0.61)	0.08 (−0.37 to 0.53)
Physical well-being (MQOL)	1–4 (4 = worst)	5.3 (2.6)	0.26 (−0.11 to 0.63)	5.3 (2.5)	0.44 (0.07 to 0.81)	−0.18 (−0.70 to 0.34)
Existential (MQOL)	1–4 (4 = worst)	7.5 (1.7)	−0.01 (−0.22 to 0.20)	7.4 (2.1)	0.08 (−0.13 to 0.29)	−0.09 (−0.38 to 0.20)
Support (MQOL)	1–4 (4 = worst)	8.8 (1.7)	−0.17 (−0.39 to 0.05)	8.5 (1.8)	−0.02 (−0.24 to 0.20)	−0.14 (−0.45 to 0.16)
Parenteral morphine equivalents, *mg/d*‡	NA	34.2 (15.3 to 83.3)	0.007 (−0.09 to 0.77)	35.8 (13.3 to 106.7)	0.11 (0.006 to 0.21)	−0.10 (−0.25 to 0.05)

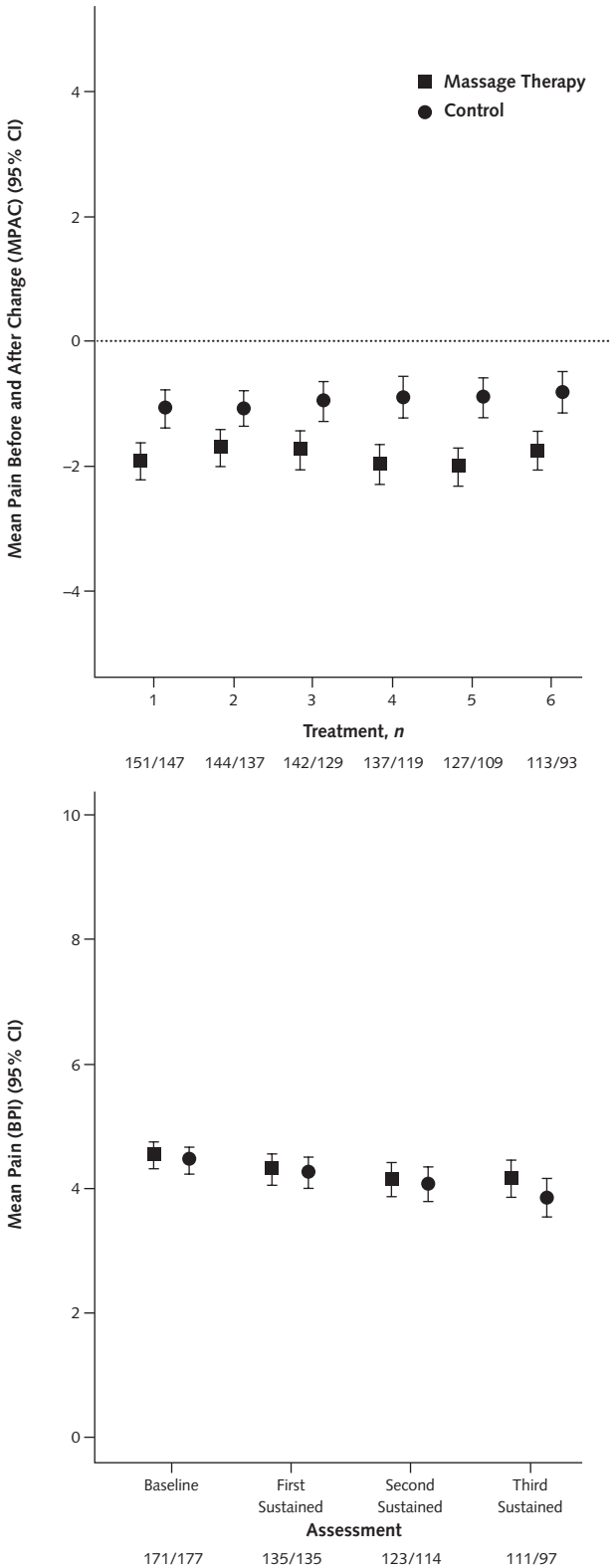
BPI = Brief Pain Inventory; MPAC = Memorial Pain Assessment Card; MQOL = McGill Quality of Life Questionnaire; MSAS = Memorial Symptom Assessment Scale; NA = not applicable.

* Mean scores (points, unless otherwise indicated) with SDs and 95% CIs shown for immediate and sustained primary and secondary study outcomes. Comparisons adjusted for age, comorbid conditions, sex, experience with massage therapy, worst pain in past week at study entry, and Karnofsky Performance Scale score. For the immediate outcomes mixed-effects models, there were 151 massage therapy patients and 147 control participants. For the sustained outcomes mixed-effects models, there were 171 massage therapy patients and 177 control participants. Mean changes for the immediate outcomes represent the mean of (before and after) assessments for all 6 treatments. Mean changes for the sustained outcomes represent the difference between the average of the 3 after-baseline assessments and the baseline mean.

† Primary outcomes.

‡ Median baseline values (25th–75th percentiles) presented.

Figure 3. **Immediate and sustained pain outcomes.**



We obtained estimates and 95% CIs from a mixed-effects model adjusted for age, comorbid conditions, sex, experience with massage therapy, worst pain in past week at study entry, and functional status (Karnofsky Performance Scale score). **Top.** Immediate outcomes: mean change in pain before and after treatment, according to treatment number and group. We measured pain before and after treatment for immediate outcomes with the Memorial Pain Assessment Card (*MPAC*) (0- to 10-point scale; 10 = worst pain). Mean pain changes for immediate outcomes are the mean changes in pain before and after assessments at each treatment visit. The number of participants (massage therapy/control) with treatments at each visit is noted below the graph. **Bottom.** Sustained outcomes: mean pain, according to assessment number and treatment group. We measured the sustained outcome of pain with the Brief Pain Inventory (*BPI*) (0- to 10-point scale; 10 = worst pain). The number of participants (massage therapy/control) with sustained assessments at each visit is noted below the graph.

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 after treatments (mean mood difference [in MPAC scores] between study groups, 0.61 point [CI, 0.35 to 0.87 points]). Heart rate and respiratory rate decreased modestly in the massage and control groups (heart rate, −4.20 beats/min [CI, −4.90 to −3.50 beats/min] and −3.28 beats/min [CI, −4.04 to −2.57 beats/min], respectively; respiratory rate, −1.46 breaths/min [CI, −1.75 to −1.17 breaths/min] and −1.15 breaths/min [CI, −1.46 to −0.84 breaths/min], respectively), with no clinically or statistically significant differences between study groups.

Both groups demonstrated statistically significant improvements in physical and emotional symptom distress and quality of life across weekly assessments; no clinically or statistically significant differences occurred between study groups (**Table 2**; **Appendix Figure**). Total parenteral morphine equivalents also did not clinically or statistically significantly change. We observed no important effect modification associated with perceived helpfulness of massage therapy, presence of neuropathic pain, or bone metastases.

Adverse Events

Mortality rates during the study were similar between study groups (26 [13.8%] deaths in the massage group vs. 33 [17.2%] deaths in the control group; $P = 0.40$). Two (1.1%) and 6 (3.1%) serious adverse events occurred in the massage and control groups, respectively ($P = 0.28$), including 1 respiratory infection and 1 gastrointestinal bleeding event in the massage group and 1 fracture, 3 pain control issues, 1 seizure, and 1 congestive heart failure diagnosis in the control group. One adverse event in each study group resulted in study participation discontinuation. Adverse events were infrequent, were similar in both groups, and did not seem to be related to treatments.

DISCUSSION

Massage seemed 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. Although clinically signifi-

cant change in symptom distress as measured by the MSAS has no definition, the observed improvements were minimal. Dispelling common concerns about the safety of massage in cancer, we found no statistically significant differences in adverse events or deaths among this advanced cancer population. This study provides a promising model for future clinical trials in the hospice and 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 the study participants' advanced disease status. Several studies have demonstrated relatively preserved quality of life and stable symptom distress among hospice and palliative care populations. None of these studies documented analgesic medication use, so whether the stable quality of life and symptoms in previous studies was due to aggressive symptom management consistent with excellent hospice and palliative care is unclear. 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 and palliative care (4, 27, 52, 53).

Previous research has supported the value of massage for relieving pain in patients with cancer, although study limitations (small sample size, lack of adequate control groups) and conflicting results made firm conclusions impossible (54–56). Although 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 reduced subjective levels of anxiety, which may be more sensitive than objective indicators of relaxation or arousal (56, 63). Given that so few randomized trials of massage therapy, particularly in this patient population, have been published, few direct comparisons are available.

The REST study suggests immediate beneficial effects of massage for pain and mood in advanced cancer; however, whether these benefits endured for hours or several days is not clear. 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 and provided comfort and relaxation, a time for reflection, and a sense of connection to another person. 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 the incorporation of randomization to a control group that was specifically designed to control for time, attention, touch, and healing intent and the study's 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 because participants self-reported most measures and treating therapists who were not blinded to treatment assignment obtained the immediate outcome measures. We addressed this issue by using previously developed scales with established reliability, validity, and sensitivity to change and by pilot-testing the instruments. Second, participants may not be representative of all patients with advanced cancer. By design, this study included only English-speaking adults with an estimated life expectancy of 3 weeks or longer who were able to participate. Participants with advanced cancer may systematically differ from those who were not approached for study participation or those who did not meet eligibility criteria. We screened 509 patients for study enrollment, which represents 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 therapy, 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 "nonmoving touch" throughout the trial. Also, we observed no association between expected helpfulness of massage and study outcomes. Third, given the nature of this patient population, we expected a substantial rate of loss to follow-up due to death or disability. We attempted to lessen the effect of potential incomplete follow-up through eligibility criteria, sample size calculation, and analytic approach, assuming that we would have a 30% loss to follow-up. In the study, 37 massage patients and 45 control participants did not receive any study treatments (21.6% combined). Seventeen massage patients and 15 control participants did not contribute any sustained outcome data (8.4% combined). Although we found few differences between those who did and those who did not receive treatments or between those who did and those who did not contribute sustained outcome data, it is possible that unmeasured systematic differences would affect study outcomes. Fourth, the study lacked a usual care control group. The control condition, which was designed as an inactive control exposure, seems to have had a beneficial effect over time similar to that of massage. However, without a usual care control group, the differential beneficial effect is not conclusive. Conducting a 3-group trial, comparing massage with a control exposure and with usual care, would be ideal but was not feasible because of the 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 to 1.5 points) are applied to the MPAC mood findings, then the immediate improvement of 1.58 points after massage would be considered clinically significant. However, the mean difference between the massage and control groups (0.61 point) would not reach the level of clinical significance. For the MSAS, the observed improvements, although statistically significant, are quite small (0.07 to 0.16 points) and probably 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 after treatment sessions. Sustained benefits of massage in this study sample are less evident. Patients with advanced cancer may be touch-deprived because of 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, which 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 that can mediate the multiple distressing symptoms encountered in advanced illness.

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Reproducible Research Statement: *Study protocol and data set*: Available from Dr. Kutner (e-mail, jean.kutner@ucdenver.edu). Massage and simple touch protocols are available online at www.annals.org (**Appendix**). *Statistical code:* Available from Dr. Fairclough (e-mail, diane.fairclough@ucdenver.edu).

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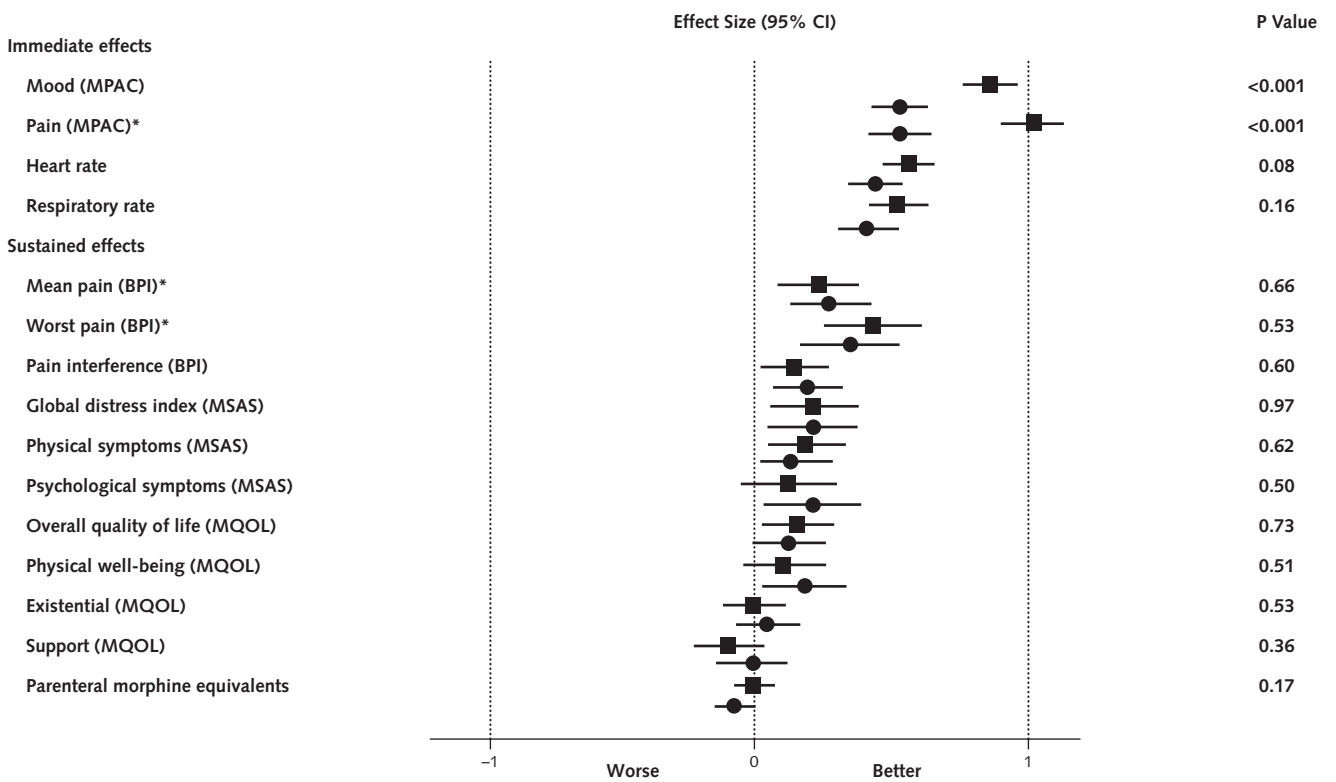
Appendix Figure. **Immediate and sustained effects.**



Effect sizes with 95% CIs and *P* values shown for study outcomes according to massage therapy (*squares*) and control (*circles*) groups. Data represent improvement if greater than 0 and worsening if less than 0. Effect sizes adjusted for age, comorbid conditions, sex, experience with massage therapy, worst pain in past week at study entry, and functional status (Karnofsky Performance Scale score). BPI = Brief Pain Inventory; MPAC = Memorial Pain Assessment Card; MQOL = McGill Quality of Life Questionnaire; MSAS = Memorial Symptom Assessment Scale.
* Primary end points.