Terapie integrative durante e dopo il trattamento per carcinoma mammario: la visione dell'American Society of Clinical Oncology (ASCO)

Camilla Lisanti

People use "integrative", "complementary" and "alternative" interchangeably, but they are not the same thing!

INTEGRATIVE MEDICINE

It coordinates use of evidence-based complementary practices and conventional care

COMPLEMENTARY MEDICINE

It comprises therapies used as a complement alongside conventional medicine

ALTERNATIVE MEDICINE

It comprises therapies used in place of conventional medicine

H. Greenlee et al. CA Cancer J Clin 2017

«How big is the matter?»

- 25% of the population in Great Britain
- 50% of the population in Germany
- 50% of the population in France
- 50% of the population in Australia
- 42% --> 69% of the population in USA

«Who gets involved?»

- More women than man
- People with higher cultural level and high income
- People who have been hospitalized in the past
- Young age
- Brief expectation of life

Gansler T et al. Cancer 2008
Boon H et al. J Clin Oncol Off J Am Soc Clin Oncol 2000

«Why would cancer patients be interested in?»

- They'd like to relieve the side effects of mainstream cancer treatment without having to take more medicine
- They are seeking a less unpleasant treatment approach that might have fewer side effects
- They want to take an active role in improving their own health and wellness
- They prefer alternative theories of health and disease, as well as alternative treatments
- Truth communicated as a ruling without appeal
- Sense of abandonment
- Ineffective communication

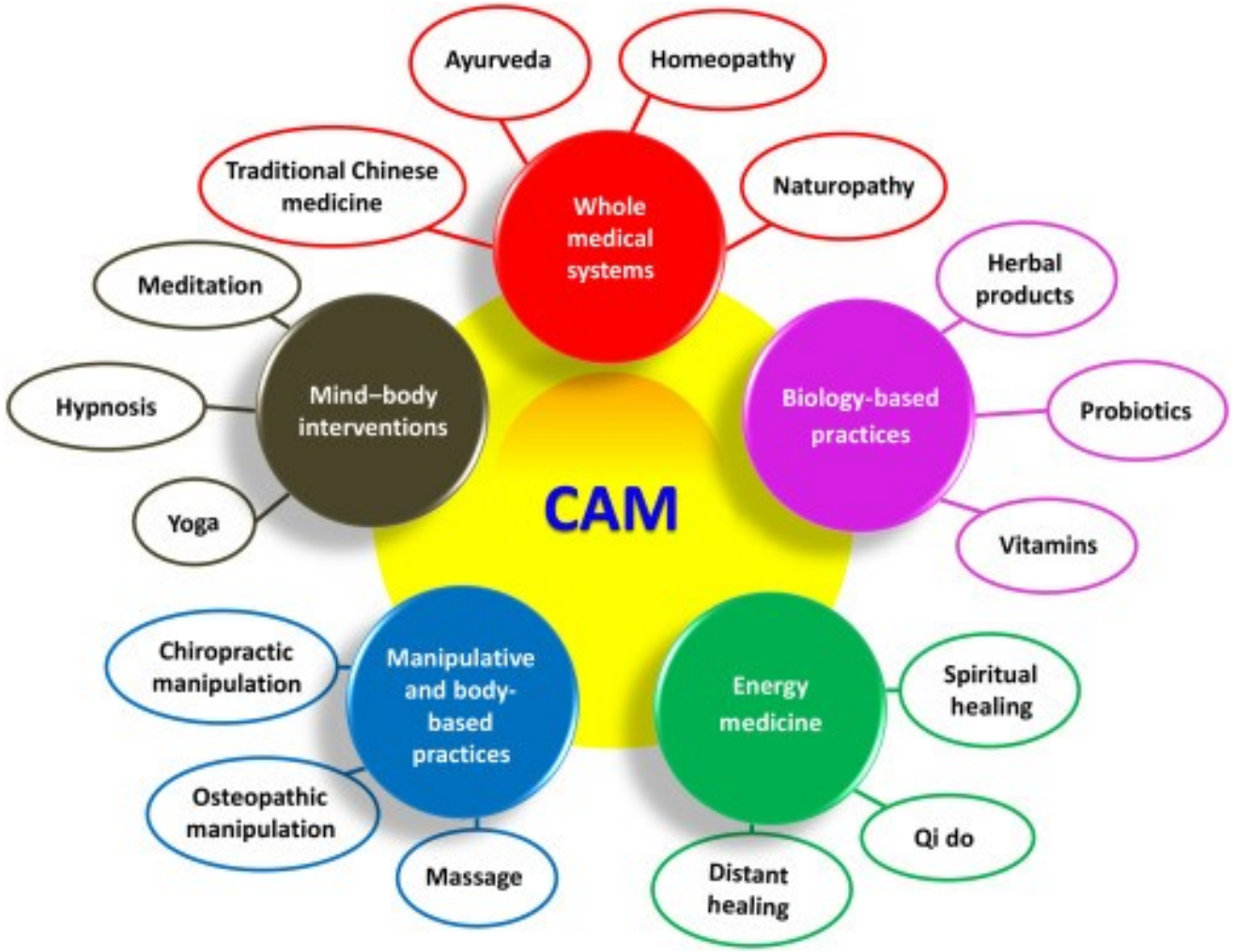
Astin JA et al. JAMA 1998
Davis EL et al. Oncologist 2012

«About breast cancer…»

- Patients with breast cancer and breast cancer survivors are frequent users of complementary a integrative therapies
- A lot of studies found that both the use of CAM products and visits to CAM practitioners by wom diagnosed with breast cancer significantly increased over the years

Use of Products	1998 N = 411	2005 N = 527	
Vitamins/Minerals[1] #	204 (49.6)	269 (51.0)‡	0.67
Herbal Remedies[2] #	101 (24.6)	194 (36.8)*	>0.01
Green tea	71 (17.3)	145 (27.5)	>0.01
Special foods/diet	63 (15.3)	140 (26.6)	>0.01
Essiac	61 (14.8)	39 (7.4)	>0.01
Meditation	42 (10.2)	60 (11.4)	0.57
Shark cartilage	22 (5.4)	16 (3.0)	0.07
Other therapies[2] §	22 (5.4)	39 (7.4)	0.21
Homeopathy	16 (3.9)	34 (6.4)	0.08
Faith healing	14 (3.4)	N/A	N/A
TCM remedy	7 (1.7)	18 (3.4)	0.11
Natural Supplements[3] #	N/A	198 (37.6)†	N/A
Soy	N/A	58 (11.0)	N/A

H. S. Boon et al. BMC Woman's Health, 2007; 7:4; doi:10.1186/1472-6874-7


CAM
Whole medical systems
Ayurveda
Homeopathy
Traditional Chinese medicine
Naturopathy
Mind–body interventions
Meditation
Hypnosis
Yoga
Biology-based practices
Herbal products
Probiotics
Vitamins
Manipulative and body-based practices
Chiropractic manipulation
Osteopathic manipulation
Massage
Energy medicine
Spiritual healing
Qi do
Distant healing


MYTHS
FACTS

Clinical practice guidelines on the evidence-based use of integrative therapies during and following breast cancer treatment

Heather Greenlee, ND, PhD, MPH, Melissa J. DuPont-Reyes, MPH, MPhil, Lynda G. Balneaves, RN, PhD, Linda E. Carlson, PhD, Misha R. Cohen, OMD, LAc, Gary Deng, MD, PhD, Jillian A. Johnson, MSc, Matthew Mumber, MD, Dugald Seely, ND, MSc, Suzanna Zick, ND, MPH, Lindsay Boyce, MLIS, and **Debu Tripathy, MD**

SIO Society for Integrative Oncology

- To update the previously published clinical practice guidelines (2014), the **SIO** expert panel conducted a systematic review of literature from January 1, 2014 through December 31, 2015:
  - ✓ Randomized controlled trials (RTCs)
  - ✓ RTCs published in English
  - ✓ RTCs included at least 50% patients with breast cancer

Table 1. Recommendation Grading System Used in the SIO Guideline[5]

Grade	Definition
A	Recommends the modality (there is high certainty that the net benefit is substantial—offer/provide this modality).
B	Recommends the modality (there is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial—offer/provide this modality).
C	Recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences (there is at least moderate certainty that the net benefit is small—offer/provide this modality for selected patients, depending on individual circumstances).
D	Recommends against the service (there is moderate or high certainty that the modality has no net benefit—discourage the use of this modality).
H	Recommends against the service (there is moderate or high certainty that the harms outweigh the benefits—discourage the use of this modality).
I	Insufficient evidence

NOTE. Grading was performed with a modified version of the US Preventive Services Task Force grading system.[6]

H. Greenlee et al. CA Cancer J Clin 2017;67:194-232; doi: 10.3322/caac.21397

CLINICAL OUTCOMES	RECOMMENDED THERAPY	STRENGTH OF EVIDENCE GRADE[b]
Acute radiation skin reaction	Aloe vera[22,23] and hyaluronic acid cream[24,25] should not be recommended for improving acute radiation skin reaction.	D
Anxiety/stress reduction	Meditation is recommended for reducing anxiety.[26-30]	A
	Music therapy is recommended for reducing anxiety.[31-35]	B
	Stress management is recommended for reducing anxiety during treatment, but longer group programs are likely better than self-administered home programs or shorter programs.[36-39]	B
	Yoga is recommended for reducing anxiety.[40-48]	B
	Acupuncture,[49-51] massage,[52-55] and relaxation[56-60] can be considered for reducing anxiety.	C
Chemotherapy-induced nausea and vomiting	Acupressure can be considered as an addition to antiemetics drugs to control nausea and vomiting during chemotherapy.[61-63]	B
	Electroacupuncture can be considered as an addition to antiemetics drugs to control vomiting during chemotherapy.[64,65]	B
	Ginger[66-68] and relaxation[59,69] can be considered as additions to antiemetic drugs to control nausea and vomiting during chemotherapy.	C
	Glutamine[70,71] should not be recommended for improving nausea and vomiting during chemotherapy.	D

H. Greenlee et al. CA Cancer J Clin 2017;67:194-232; doi: 10.3322/caac.21397

Depression/mood disturbance	Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms.[26-30,72-76]	A
	Relaxation is recommended for improving mood disturbance and depressive symptoms.[56,59,60,69,77,78]	A
	Yoga is recommended for improving mood and depressive symptoms.[40-43,45-48,79-85]	B
	Massage is recommended for improving mood disturbance.[53-55,86-88]	B
	Music therapy is recommended for improving mood.[33,35,89,90]	B
	Acupuncture,[49-51,91,92] healing touch,[93,94] and stress management[36-38,95,96] can be considered for improving mood disturbance and depressive symptoms.	C
Fatigue	Hypnosis[97,98] and ginseng[99,100] can be considered for improving fatigue during treatment.	C
	Acupuncture[51,101-103] and yoga[45,80,84,104-106] can be considered for improving post-treatment fatigue.	C
	Acetyl-L-carnitine[107] and guarana[108,109] should not be recommended for improving fatigue during treatment.	D
Lymphedema	Low-level laser therapy,[110,111] manual lymphatic drainage,[112-118] and compression bandaging[114-116] can be considered for improving lymphedema.	C
Neuropathy	Acetyl-L-carnitine is not recommended for the prevention of chemotherapy-induced peripheral neuropathy in patients with BC due to potential harm.[107]	H
Pain	Acupuncture,[119-124] healing touch,[93] hypnosis,[125,126] and music therapy[31,34] can be considered for the management of pain.	C
Quality of life	Meditation is recommended for improving quality of life.[27-29,73-75,127]	A
	Yoga is recommended for improving quality of life.[43,46-48,82-85,104-106,128]	B
	Acupuncture,[49,51,102,129,130] mistletoe,[131-134] qigong,[135,136] reflexology,[137-139] and stress management[36-38,95,96,140,141] can be considered for improving quality of life.	C
Sleep disturbance	Gentle yoga[45,48,79,84,142] can be considered for improving sleep.	C
Vasomotor/hot flashes	Acupuncture[49,91,92,143-148] can be considered for improving hot flashes.	C
	Soy[149-151] is not recommended for hot flashes in patients with BC due to lack of effect.	D

VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline

Gary H. Lyman, Heather Greenlee, Kari Bohlke, Ting Bao, Angela M. DeMichele, Gary E. Deng, Judith M. Fouladbakhsh, Brigitte Gil, Dawn L. Hershman, Sami Mansfield, Dawn M. Mussallem, Karen M. Mustian, Erin Price, Susan Rafte, and Lorenzo Cohen

- The **ASCO** Expert Panel also carefully reviewed the SIO guidelines content to determine appropriateness for ASCO endorsement

"Recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients"

- Overall, the **ASCO** Expert Panel agrees with the recommendations as stated in the guideline, with some discussion points.

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline/1

Chemotherapy-Induced Nausea and Vomiting

- Acupressure can be considered as an addition to antiemetic drugs to control nausea and vomiting during chemotherapy. (Grade B)
- Electroacupuncture can be considered as an addition to antiemetic drugs to control vomiting during chemotherapy. (Grade B)
- Ginger and relaxation can be considered as additions to antiemetic drugs to control nausea and vomiting during chemotherapy. (Grade C)
- Glutamine should not be recommended for improving nausea and vomiting during chemotherapy. (Grade D)

ASCO Discussion Point: the Grade B recommendations differ from the 2017 ASCO antiemetic guidelines: the **ASCO** Expert Panel feels that Grade C would be more appropriate!

- Trials conducted before current pharmacologic antiemetic regimens became available
- Small sample size
- Not clear evalutation of side effects of these procedures

G. H. Lyman et al. JCO September 2018; vol. 36, n° 25

Electroacupuncture for Control of Myeloablative Chemotherapy–Induced Emesis

A Randomized Controlled Trial

Female BC resected pts, Karnofsky PS ≥80, candidates for myeloablative chemotherapy *(cyclophosphamide, cisplatin and carmustine)* (n=104)

- Antiemetics drugs + Electroacupunture
- Antiemetic drugs + minimal needling
- Antiemetics drugs alone

- Electroacupunture and minimal needling started within 2 hours before the initial of chemotherapy infusion (30 min)
- Antiemetics drugs: prochlorperazine, lorazepam and diphenhydramine
  - ✓ Rescue antiemetic medications were available (i.g. metoclopramide, droperidol)
- Patients evaluation: 5 and 14 days

	Electroacupuncture Group (n = 37)	Minimal Needling Group (n = 33)	Pharmacotherapy Only Group (n = 34)
Study Period (Days 1-5)			
No. of emesis episodes per person			
Median (range)	5 (1-25)	10 (3-24)	15 (0-25)
Mean (95% CI)†	6.29 (4.20-7.02)	10.73 (7.38-11.90)	13.41 (9.55-15.05
Percent emesis-free days			
Mean (95% CI)	55 (47-63)	29 (20-37)	20 (11-29)
Follow-up Period (Days 6-14)			
No. of emesis episodes per person			
Median (range)	4 (0-32)	7 (0-30)	8 (0-22)
Mean (95% CI)†	6.89 (3.65-7.34)	8.60 (4.84-9.42)	8.56 (5.29-9.48)
Percent emesis-free days, mean (95% CI)	60 (52-68)	53 (45-62)	52 (44-62)

J. Shen et al. JAMA December 6, 2000; vol. 284, n° 21

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline/2

Depression and Mood Disturbance

- Meditation, particularly mindfulness-based stress reduction, is recommended for treating mood disturbance and depressive symptoms. (Grade A)
- Relaxation is recommended for improving mood disturbance and depressive symptoms. (Grade A)
- Yoga is recommended for improving mood disturbance and depressive symptoms. (Grade B)
- Massage is recommended for improving mood disturbance. (Grade B)
- Music therapy is recommended for improving mood disturbance. (Grade B)
- Acupuncture, healing touch, and stress management can be considered for improving mood disturbance and depressive symptoms. (Grade C)

Fatigue

- Hypnosis and ginseng can be considered for improving fatigue during treatment. (Grade C)
- Acupuncture and yoga can be considered for improving post-treatment fatigue. (Grade C)
- Acetyl-L-carnitine and guarana should not be recommended for improving fatigue during treatment. (Grade D)

ASCO Discussion Point: the safety and efficacy of ginseng may vary by type of ginseng; some ginseng preparations may have estrogenic properties (> those derived from ethanol extracts). The ginseng studies cited by the SIO guideline used *American ginseng* (Panax quinquefolius) that was tested for quality and potency; the duration of treatment in these studies was short (8 weeks), and its safety and efficacy over longer periods remains uncertain.

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline/3

Sleep Disturbance

- Gentle yoga can be considered for improving sleep. (Grade C)

Lymphedema

- Low-level laser therapy, manual lymphatic drainage, and compression bandaging can be considered for improving lymphedema. (Grade C)

Neuropathy

- Acetyl-L-carnitine is not recommended for the prevention of chemotherapy-induced peripheral neuropathy in patients with breast cancer due to potential harm. (Grade H)

Pain

- Acupuncture, healing touch, hypnosis, and music therapy can be considered for the management of pain. (Grade C)

Quality of Life

- Meditation is recommended for improving quality of life. (Grade A)
- Yoga is recommended for improving quality of life. (Grade B)
- Acupuncture, mistletoe, qigong, reflexology, and stress management can be considered for improving quality of life. (Grade C)

ASCO Discussion Point: The mistletoe trials cited by the SIO guidelines evaluated subcutaneous delivery only, that is not currently approved by FDA. Orally available mistletoe is available in the United States, but ingestion of high doses of mistletoe berry or leaf is known to cause serious adverse reactions (i.e. gastrointestinal disorder, bradycardia, illusions, death)

- To update the SIO literature analyzed in clinical practice guidelines published in 2017, the **ASCO** expert panel conducted a systematic review of literature from January 1, 2016 through December 15, 2017:
  - ✓ Randomized controlled trials (RTCs)
  - ✓ RTCs published in English

- The updated search yielded 167 records, 30 of which were potentially eligible for inclusion based on title and abstract review

- Potentially eligible publications were reviewed by one of the SIO guideline panel members, and **9** were shared with the ASCO Expert Panel for further discussion

These publications do not lead to substantive modifications of the SIO recommendations but in general they support, and in some cases may strengthen, current recommendations

Pain, AIs-induced arthralgias	Vasomotor symptoms	Lymphedema
Quality of life	Acute radiation skin reactions	Sleep disturbance
Pain	Neuropathy	Fatigue

Pain, AIs-induced arthralgias

- Aromatase inhibitors (AIs) have proven efficacy for the treatment of hormone-sensitive breast cancer
- However, many patients (50%) experience side effects,including aromatase inhibitor–related arthralgias (pain and stiffness), which contribute to non-adherence with therapy
- Data from clinical trials suggest that non-adherence to endocrine therapy is associated with reduced disease-free survival (DFS)
- *Duloxetine* is the only drug that has shown a statistical and clinical benefit in this setting *(randomized, multicenter, placebo-controlled clinical trial)*
- Several trials have evaluated other approaches, such as **acupuncture**, as a treatment for AIs-related arthralgias

NL Henry et al. SWOG S1202. JCO 2018; 36(4): 326-332
DL Hershman et al. JAMA July 10, 2018; vol. 320, n° 2

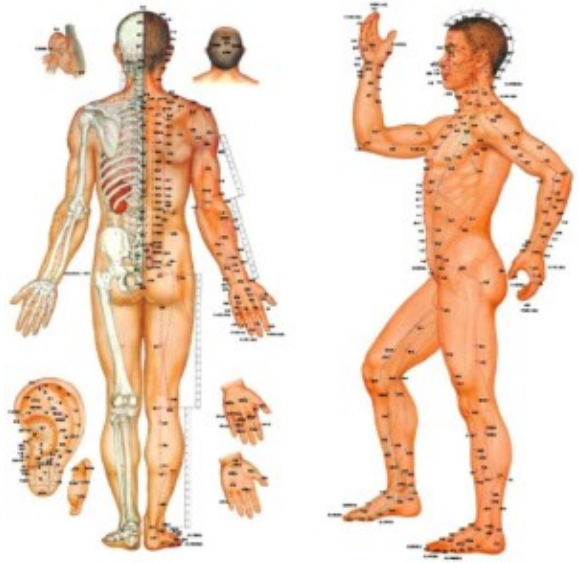
Acupuncture

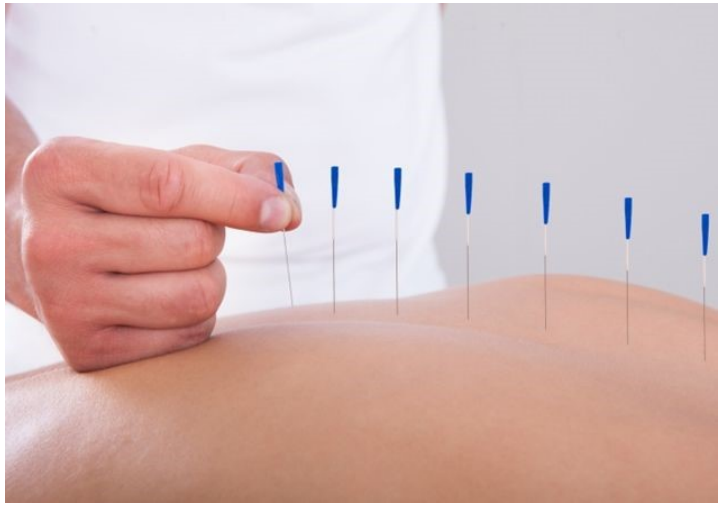
- It is a traditional Chinese therapy that involves insertion of fine, single-use, sterile needles in acupoints according to a system of channels and meridians that were developed by early practitioners of Traditional Chinese Medicine

- The needles are stimulated by manual manipulation, electrical stimulation (**electroacupuncture**), or heat

- Several small studies have suggested that acupuncture may be beneficial for AIs-related arthralgias; however others have shown no benefit

- The overall interpretation of these trials has been uncertain due to:
  - short duration
  - small sample sizes
  - differences in methodology





JH Chirgwin et al. JCO 2016
DL Hershman et al. JAMA July 10, 2018

JAMA | Original Investigation

Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer
A Randomized Clinical Trial

Dawn L. Hershman, MD, MS; Joseph M. Unger, PhD, MS; Heather Greenlee, ND, PhD; Jillian L. Capodice, MS, LAc; Danika L. Lew, MA; Amy K. Darke, MS; Alice T. Kengla, MD; Marianne K. Melnik, MD; Carla W. Jorgensen, MD; William H. Kreisle, MD; Lori M. Minasian, MD; Michael J. Fisch, MD; N. Lynn Henry, MD; Katherine D. Crew, MD, MS

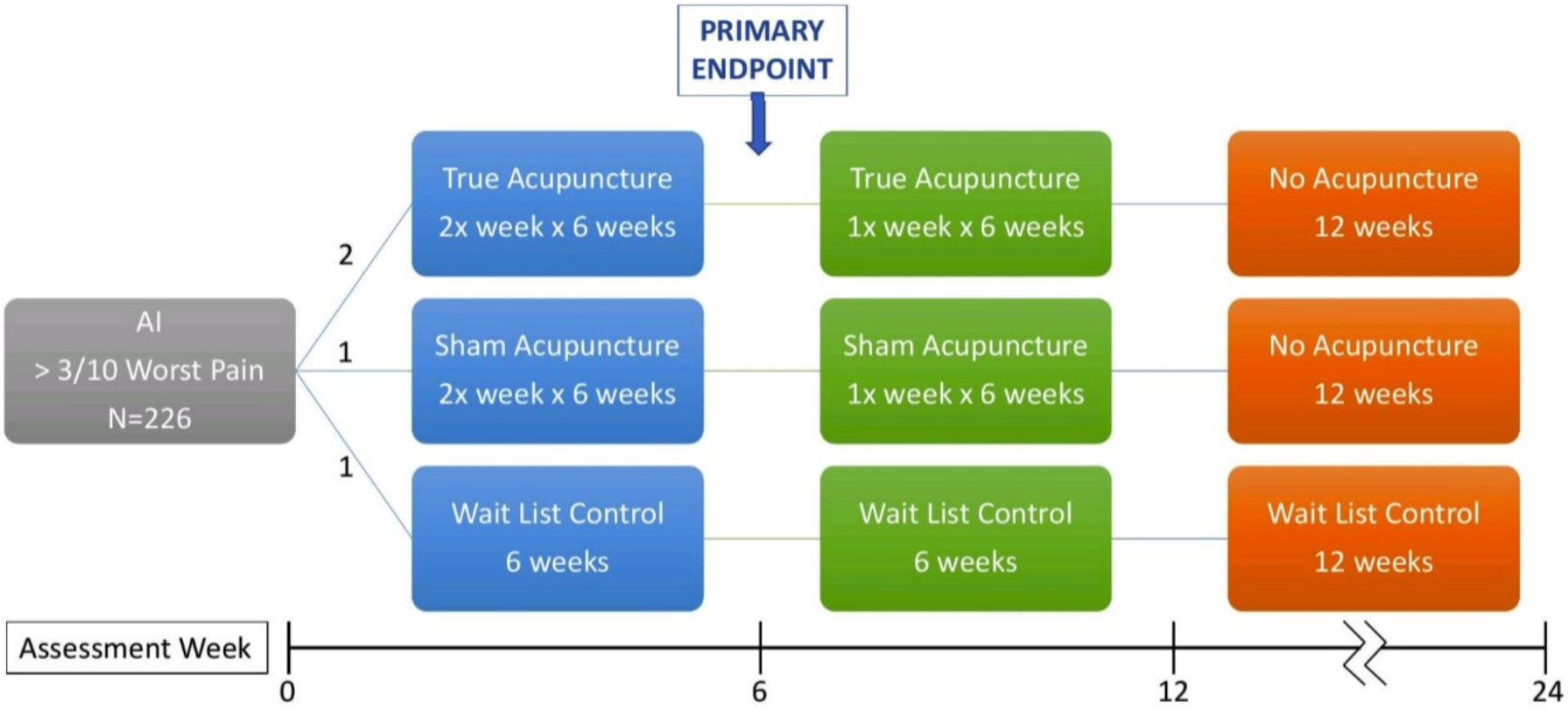
SAN ANTONIO BREAST CANCER SYMPOSIUM® 2017

- Multicenter (11), randomized (2:1:1), blinded sham- and waitlist controlled clinical trial

- Main inclusion criteria:
  - ✓ Women with histologically confirmed (stages I-III) primary invasive ER/PgR–positive BC
  - ✓ Postmenopausal or premenopausal (with use of a gonado tropin-releasing hormone agonist)
  - ✓ To be taking a third generation AIs for >30 days prior to registration, with plans to continue for at least 1 additional year
  - ✓ A score of greater than 3 (range,0-10; higher scores indicate greater pain) on the worst pain item of the Brief Pain Inventory-Short Form(BPI-SF) that (by patient report) started or increased since starting AIs therapy

- The primary hypothesis was that true acupuncture would decrease joint pain associated with the use of AIs compared with **both** sham acupuncture or wait list control at 6 weeks

- **Primary endpoint:** **BPI Worst Pain Item (BPI-WP) score at 6 weeks of treatment** (a reduction of 2 points on the BPI-WP has been identified as a clinically meaningful change for patients)



- **True Acupuncture**
  - Standard Traditional Chinese Medicine point prescription to reduce pain and decrease stress (30-45 min per session)
  - Full body, auricular and joint-specific acupuncture protocol tailored to the most painful joints
- **Sham Acupuncture**
  - Shallow needle insertion utilizing thin and short needles at non-acupuncture points
  - Four standardized points, auricular sham and joint-specific sham point protocols within the proximity of the specified anatomic area
- **Wait List Control**
  - True acupuncture offered after 24 weeks

- From March 2012 to February 2017 a total of 226 patients were enrolled

	Total (n=226)		True Acupuncture (n=110)		Sham Acupuncture (n=59)		Waitlist Control (n=57)	
Age, years								
Median	60.7		60.8		57.0		60.6	
Hispanic, N (%)	21	7%	11	10%	7	12%	3	5%
Race, N (%)								
White	193	88%	88	83%	54	93%	51	91%
Black	10	5%	6	6%	2	3%	2	4%
Asian	15	7%	11	10%	2	3%	2	4%
Prior Chemotherapy, N (%)	111	49%	56	51%	31	53%	24	42%
AI Therapy (median yrs)	1.1		1.0		1.1		1.1	
Prior Acupuncture, N (%)	44	19%	19	17%	13	22%	12	21%
Baseline Score – BPI WP			6.84		6.55		6.48	

❖ Primary endpoint: BPI Worst Pain Item (BPI-WP) score at 6 weeks of treatment

Analysis by Group	No. of Patients	Group Mean Difference[a] Mean (95% CI) Baseline[c]	Follow-up	Fitted Difference (95% CI) True vs Sham True vs Waitlist	*P* Value
Worst Pain[d]					
Week 6[e]					
True	100	6.84 (6.55 to 7.13)	4.79 (4.36 to 5.22)		
Sham	54	6.55 (6.14 to 6.98)	5.48 (4.78 to 6.18)	0.92 (0.20 to 1.65)	.01
Waitlist	51	6.48 (6.07 to 6.89)	5.49 (4.81 to 6.17)	0.96 (0.24 to 1.67)	.01
Week 12					
True	101	6.84 (6.55 to 7.13)	4.53 (4.05 to 5.01)		
Sham	54	6.55 (6.14 to 6.98)	5.04 (4.3		
Waitlist	51	6.48 (6.07 to 6.89)	6.29 (5.7		

Analysis by Group	No. of Patients	Group Mean Difference[a] Mean (95% CI) Baseline[c]	Follow-up	Fitted Difference (95% CI) True vs Sham True vs Waitlist	*P* Value
Worst Stiffness					
Week 6					
True	100	6.65 (6.26 to 7.04)	4.46 (3.94 to 4.98)		
Sham	54	6.59 (6.03 to 7.16)	5.50 (4.86 to 6.14)	1.00 (0.19 to 1.81)	.02
Waitlist	51	6.68 (6.26 to 7.10)	5.53 (4.91 to 6.14)	1.09 (0.26 to 1.92)	.01
Week 12					
True	100	6.65 (6.26 to 7.04)	4.35 (3.82 to 4.88)		
Sham	54	6.59 (6.03 to 7.16)	5.07 (4.47 to 5.68)	0.72 (−0.08 to 1.53)	.08
Waitlist	51	6.68 (6.26 to 7.10)	6.12 (5.59 to 6.64)	1.80 (1.03 to 2.57)	<.001

❖ *«Taking a look at the safety analyses»*

	True Acupuncture (n=106) Grade				Sham Acupuncture (n=55) Grade			
ADVERSE EVENTS	0	1	2	3	0	1	2	3
Bruising	**56**	**50**	0	0	**41**	**14**	0	0
Dizziness	101	5	0	0	55	0	0	0
Ear pain	105	1	0	0	54	1	0	0
Hematoma	105	1	0	0	55	0	0	0
Bleeding at injection site	103	3	0	0	53	2	0	0
Pain in extremity	105	1	0	0	55	0	0	0
Presyncope	105	0	1	0	54	0	1	0

DL Hershman et al. JAMA July 10, 2018; vol. 320, n° 2

- In this clinical trial there were statistically significant but modest improvements in pain scores with true acupuncture administered twice a week for 6 weeks compared with both sham acupuncture and wait list control

- However, the magnitude of the effect did not achieve the prespecified between-group difference of 2 points in the primary end-point of BPI-WP

Conclusion

Among postmenopausal women with early-stage breast cancer and aromatase inhibitor-related arthralgias, true acupuncture compared with sham acupuncture or with waitlist control, resulted in a statistically significant reduction in joint pain at 6 weeks, although the observed improvement was of uncertain clinical importance.

"How does AIOM think?"

Associazione Italiana di Oncologia Medica

RACCOMANDAZIONE

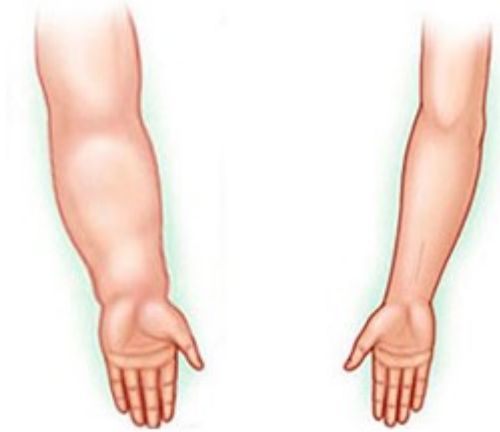
Qualità dell'evidenza	Raccomandazione clinica	Forza della raccomandazione
BASSA	Le artralgie in corso di terapia con inibitori delle aromatasi possono essere trattate con agopuntura manuale) (Crew 2010, Hershaw 2018, Roberts 2017)	**Positiva debole**

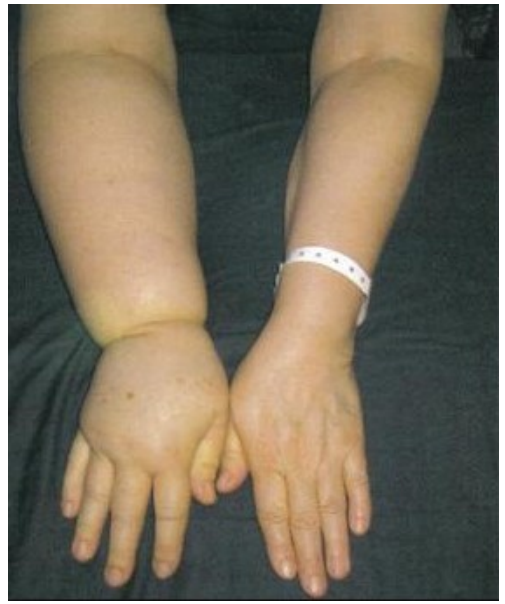
Lymphedema

- **ULL** is the abnormal accumulation of protein-rich fluid within the interstitial space of the ipsilateral upper limb

- Upper limb lymphedema (**ULL**) is a common complication after radical mastectomy and or radiation of the axillary lymph nodes in patients with BC (30%–50%) → **"socio-economical problem"**

- **ULL** can be considered
  - ✓ Acute (within 18 months from surgery)
    - transient
    - reversible
    - resolved through multiple decongestive approaches *[i.g. manual lymph drainage (MLD) massage, compression bandage, and physical exercise]*
  - ✓ Chronic (after 18 months from surgery)
    - more severe
    - progressive pain
    - swelling
    - recurrent infection
    - upper extremity dysfunction
    - recalcitrant to the common effective decongestive



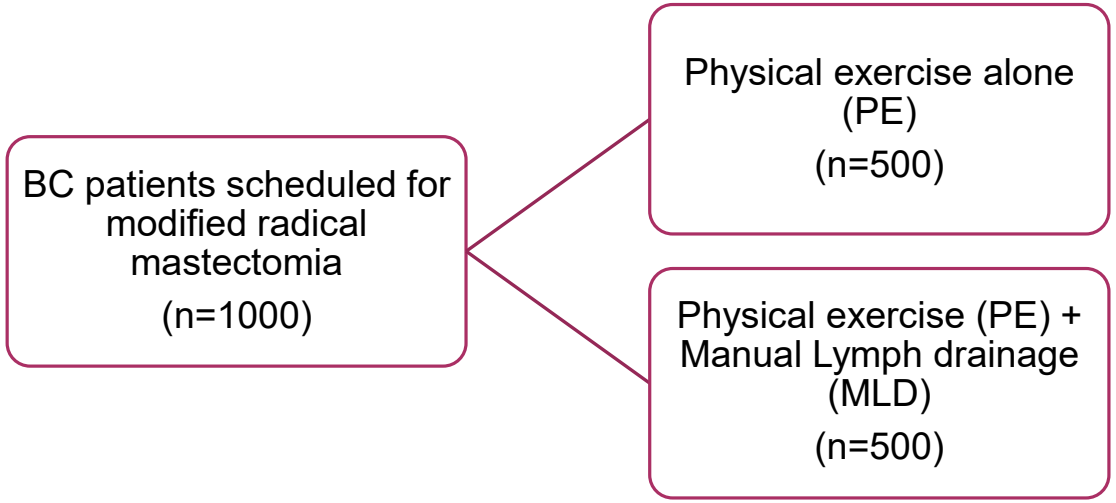


L. Zhang et al. Lymphatic Research and Biology 2016; vol. 14, n° 2

Combining Manual Lymph Drainage with Physical Exercise after Modified Radical Mastectomy Effectively Prevents Upper Limb Lymphedema

Lijuan Zhang, BS,[1#] Aiqun Fan, BS,[1#] Jun Yan, BS, PhD,[2] Yan He, BS,[1] Huiting Zhang, BS,[1] Huizhen Zhang, BS,[1] Qiaoling Zhong, BS,[1] Feng Liu, BS,[1] Qinghua Luo, BS,[1] Liping Zhang, BS,[1] Hailin Tang, BS, PhD,[1] and Mingzhu Xin, BS[1]

- **Aim of this study**: «evaluated MLD in combination with physical exercise, for the prevention of acute ULL in breast cancer patients after modified radical mastectomy, compared to physical exercise alone"
- Between May 2012 and October 2014, 1000 Chinese women were recruited into this randomized (1:1) clinical trial



- **Procedures details**:
  - ✓ **PE**:
    1) within the first 7 days after surgery (before removal of the drainage tube): passive exercise
    2) between removal of the drainage tube and the surgical sutures (at 7–30 days): active exercise on the affected upper limb
    3) after removal of the surgical sutures, extensive active exercise involving the affected shoulder: 3 sessions/day, 15min/session.
    4) all patients continue the remedial exercise for 6 months after the surgery.

  - ✓ **MLD**: after suture removal and closure of the incision, the patients were trained to perform self-MLD 3 times/day (early morning, early afternoon, and evening) and for 30 min each session. Each session was further divided into 3 sequential steps (10min/step):
    1) to activate lymph vessels
    2) to soften scar tissue
    3) to stimulate lymphdrainage

- ULL was assessed for each patients by tapemeasuring:
  - ✓ 24 hours before surgery
  - ✓ 1, 3, 6 and 12 months afterward

- **ULL evaluated parameters**:
  - ✓ Status of scar deformation
  - ✓ Extent of lymphedema
  - ✓ Maximum shoulder abduction

	PE (n = *500*)	*MLD* (n = *500*)	P *values*
Age (years)			0.376
<50	272	266	
≥50	228	234	
Pathological subtypes			0.084
IDC[a]	303	324	
Others	197	176	
Differentiation			0.096
Well	122	147	
Moderate	269	222	
Poor	109	131	
Tumor-node-metastasis staging			0.201
I+II	211	197	
III	289	303	
Estrogen receptor status			0.151
+	293	310	
–	207	190	
Progesterone receptor status			0.075
+	358	336	
–	142	164	
HER2 status			0.177
+	332	317	
–	168	183	
Lymph node metastasis			0.125
+	296	277	
–	204	223	

[a]IDC, invasive ductal carcinoma.

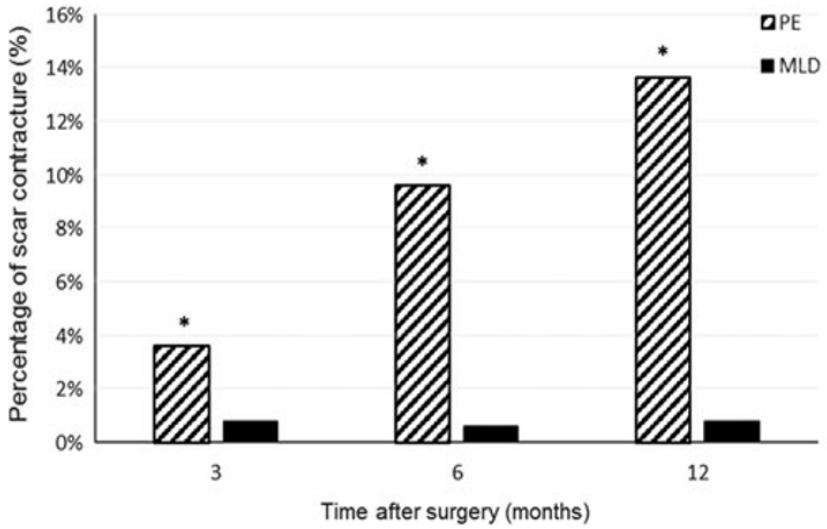


FIG. 1. Percentage of scar contracture during the 1-year follow-up in the MLD and PE and MLD groups. *$p < 0.05$, MLD *vs*. PE group.

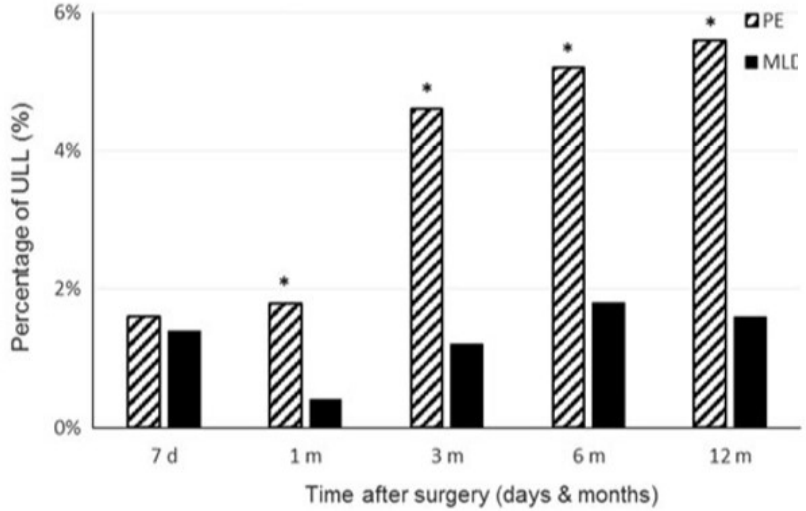


FIG. 2. Percentage of ULL during the 1-year follow-up in the MLD and PE groups. *$p < 0.05$, MLD *vs*. PE group.

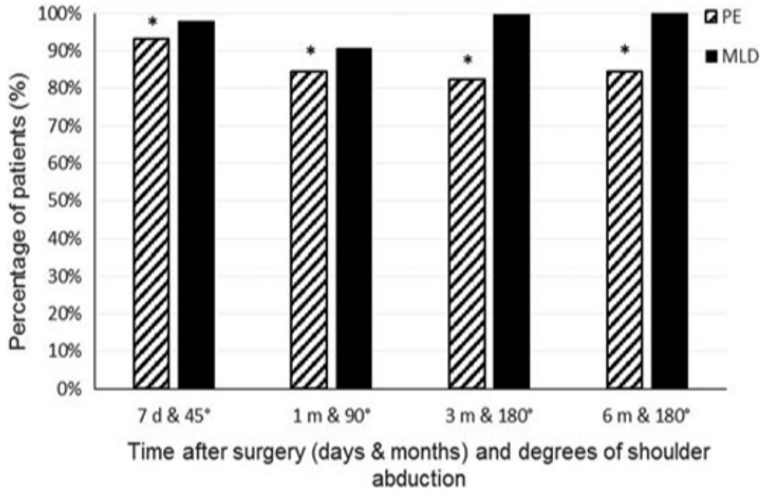


FIG. 3. Percentage of patients achieving indicated degrees of shoulder abduction during the 1-year follow-up in the MLD and PE groups. *$p < 0.05$, MLD *vs*. PE group.

- At present, complete decongestive therapy (**CDT**) has been proposed as standard care for lymphedema

- CDT is a multi-modality therapeutic program that comprises MLD, short-stretch compression bandaging, lymphatic exercise, skin care, and sometimes intermittent pneumatic compression

- **MLD** is a light, hands-on technique. It differs from deep muscular or myofascial massage because it works on superficial lymphatic vessels

↓

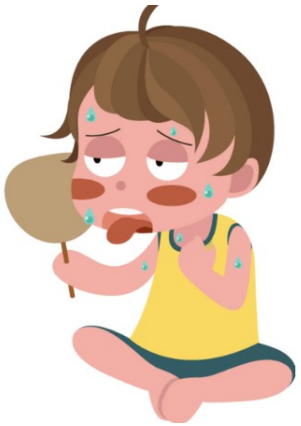
"the excess interstitial fluid drains into the blood system"

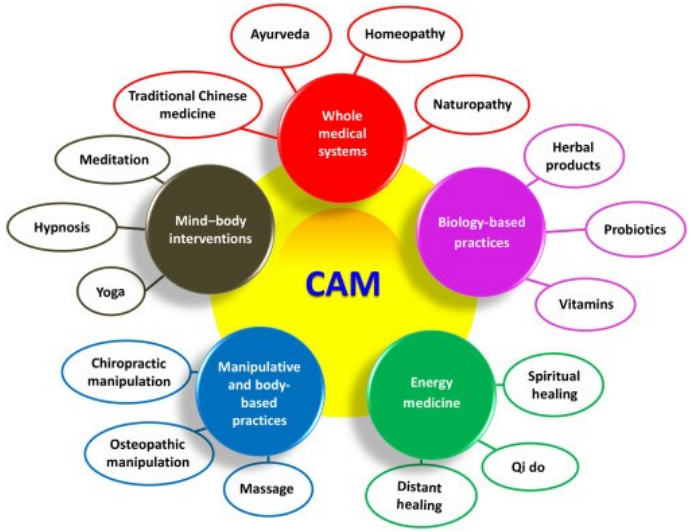
A "recent" study showed that MLD does not increase the risk of BC recurrence in patients with BC-related lymphedema

PC Hsiao et al. Ther Clinical Risk Manag 2015; 11:349-358
L. Zhang et al. Lymphatic Research and Biology 2016; vol. 14, n° 2

Vasomotor symptoms/Hot flashes

- BC patients have a higher incidence of bothersome hot flashes and climacteric syndrome than other women
- Hot flashes are more severe and longer lasting in BC women than in healthy postmenopausal women
- Adjuvant therapy often aggravates hot flashes and sweating, interfering with activities and sleep and ultimately leading to poor quality of life
- Because hormone replacement therapy is contraindicated for these women, they have limited treatment options for menopausal symptoms:
  - ✓ antidepressant drugs *(venlafaxina)*
  - ✓ self-care indications *(i.e. increased fruit and vegetable intake, reduced caffeine and alcohol intake, and more regular exercise)*





G. Lesi et al. JCO May 2016; vol. 34, n° 15

- **Acupuncture** is one of the most frequently used complementary therapies
- Although several clinical trials have shown some effects of acupuncture on vasomotor symptoms in both healthy women and women with BC, these results have been considered promising rather than conclusive in terms of efficacy
- In addition, there is a lack of systematic, well-conducted research investigating the effects of acupuncture treatment on hot flashes

VOLUME 34 · NUMBER 15 · MAY 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

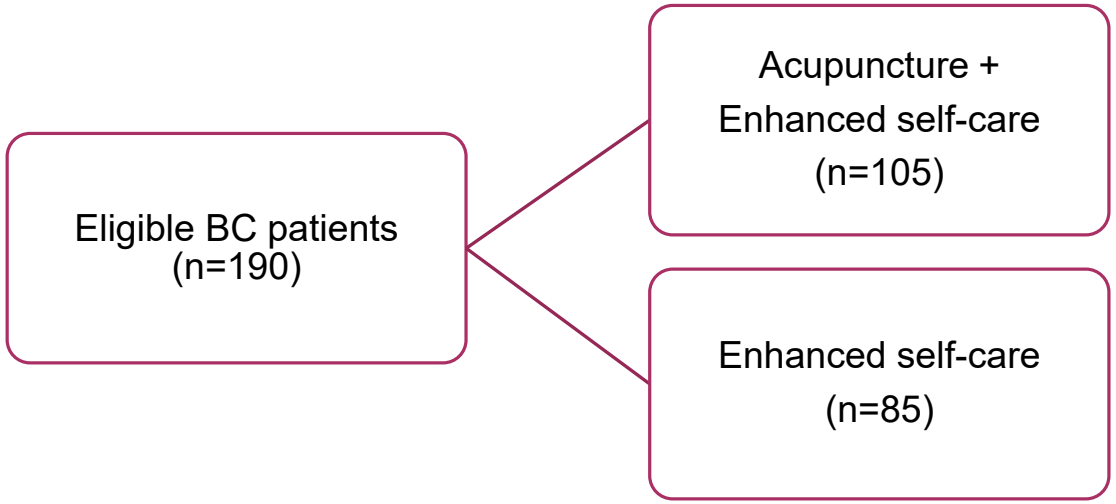
Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT)

Grazia Lesi, Giorgia Razzini, Muriel Assunta Musti, Elisa Stivanello, Chiara Petrucci, Benedetta Benedetti, Ermanno Rondini, Maria Bernadette Ligabue, Laura Scaltriti, Alberto Botti, Fabrizio Artioli, Pamela Mancuso, Francesco Cardini, and Paolo Pandolfi

Acupuncture As an Integrative Approach for the Treatment of Hot Flashes in Women With Breast Cancer: A Prospective Multicenter Randomized Controlled Trial (AcCliMaT)

- Multicenter, randomized (1:1), controlled trial
- From March 2010 to October 2013 190 patients were enrolled

- Main inclusion criteria:
  - ✓ BC patients (age 18 to 65 years) intention to continue hormonal treatment throughout the study (for patients receiving this treatment)
  - ✓ spontaneous or induced amenorrhea for at least 6 months
  - ✓ mean n° ≥6 hot flashes and/or daily mean score of 15 or greater on the Greene Climacteric Scale (GCS) during the week before enrollment
  - ✓ vasomotor syndromes for at least 6 weeks



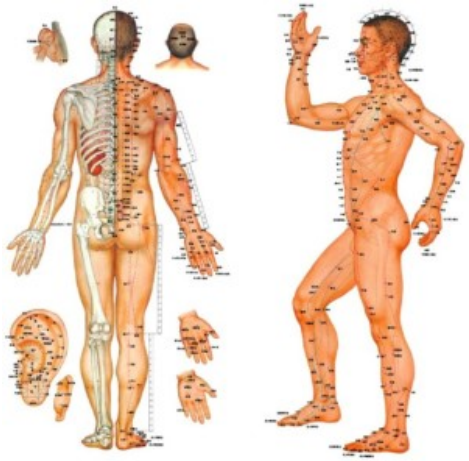
- Stratified randomization (hormonal therapy)
- Slow accrual

❖ **Procedures details** (within 2 weeks of random assignment):

- ✓ **Enhanced self-care:** (detailed information booklet) included details about hot flashes and cancer and recommendations on:
  - diet
  - physical exercise
  - eventual psychological support

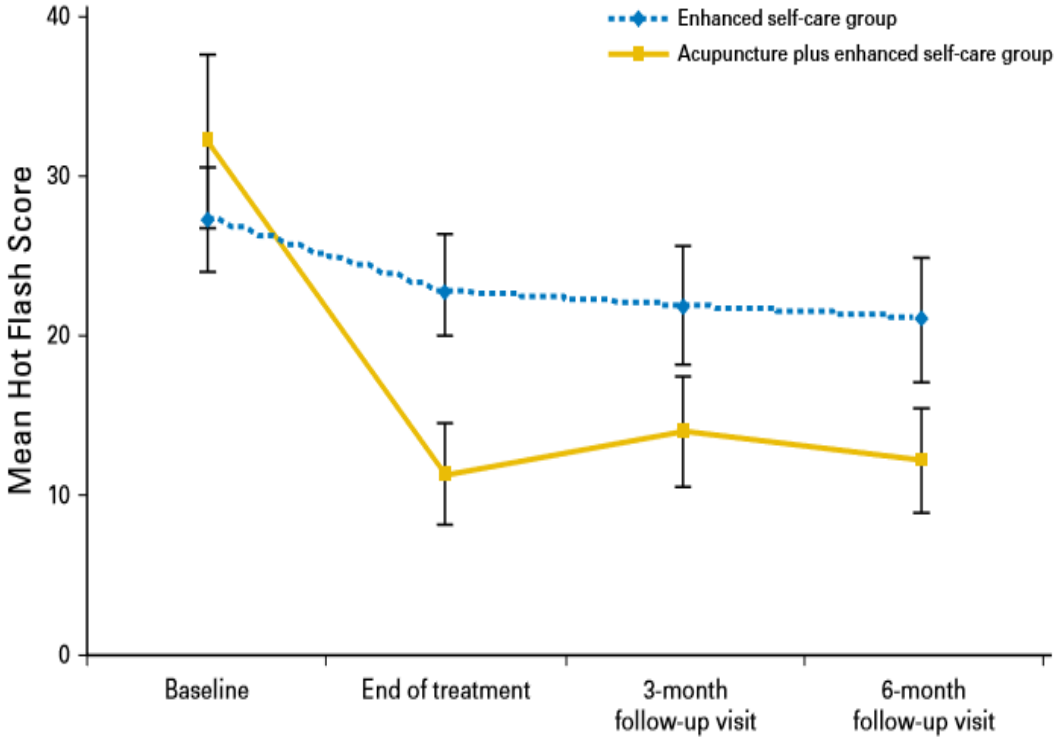
  Follow for at least 12 weeks from random assignment

- ✓ **Acupuncture**: 10 traditional Chinese medicine (TCM) acupuncture sessions (20 min) 1 per week for 12 weeks.
  - At the beginning of each acupuncture session, a TCM evaluation of the tongue and radial pulses was performed to identify the prevailing syndrome and consequently choose appropriate acupoints in addition to 3 common acupoints.
  - In some cases, supplementary points were punctured, but no more than 11 acupoints were used for each session



- **Aim of this study**: «to investigate the effectiveness of an integrative approach using acupuncture plus enhanced self-care versus enhanced self-care alone for the management of hot flashes in women with breast cancer»

- **Primary endpoint:** **<u>daily mean hot flash score (HFS) assessed at week 12</u>**
  - HFS was calculated by multiplying the mean number of daily hot flashes that occurred during the week before assessment by the mean daily severity (1, mild; 2, moderate; 3, severe)



❖ Hot Flash Score, Climateric Syndrome, and Quality of Life Outcomes at End of Treatment (week 12) and at 3- and 6-Month Follow-Up Visits by Group

Outcome	Enhanced Self-Care Group (n = 105) Mean	SD	Acupuncture Plus Enhanced Self-Care Group (n = 85) Mean	SD	Difference Between Groups (Δ)	95% CI	*P*
Hot flash score							
Week 12	22.70	19.40	11.34	14.75	−11.36	−16.39 to −6.33	.000
3-month follow-up	21.88	18.95	14.02	16.31	−7.86	−12.99 to −2.73	.0028
6-month follow-up	21.03	20.06	12.20	15.40	−8.82	−14.04 to −3.61	.001
Greene Climacteric Scale							
Week 12	18.30	9.99	11.52	7.37	−6.78	−9.35 to −4.21	.000
3-month follow-up	17.17	9.35	13.47	8.96	−3.70	−6.34 to −1.06	.0063
6-month follow-up	17.26	8.16	12.57	8.16	−4.70	−7.35 to −2.04	< .001
Menopause Quality of Life							
Vasomotor domain							
Week 12	5.94	1.56	4.36	1.68	−1.58	−2.05 to −1.12	.000
3-month follow-up	5.61	1.65	4.33	1.65	−1.28	−1.76 to −0.81	.000
6-month follow-up	5.60	1.75	4.23	1.76	−1.38	−1.88 to −0.87	.000
Psychosocial domain							
Week 12	3.76	1.65	2.96	1.52	−0.79	−1.25 to −0.34	< .001
3-month follow-up	3.60	1.66	2.90	1.60	−0.70	−1.17 to −0.23	.0039
6-month follow-up	3.67	1.83	2.96	1.69	−0.71	−1.22 to −020	.0064
Physical domain							
Week 12	3.56	1.47	2.89	1.08	−0.67	−1.05 to −0.29	< .001
3-month follow-up	3.50	1.51	3.01	1.38	−0.49	−0.91 to −0.07	.02
6-month follow-up	3.51	1.54	3.02	1.40	−0.50	−0.92 to −0.07	.02
Sexual domain							
Week 12	3.52	2.10	3.18	2.06	−0.34	−0.94 to 0.26	.25
3-month follow-up	3.47	2.14	3.37	2.13	−0.10	−0.71 to 0.52	.75
6-month follow-up	3.70	2.22	3.15	2.06	−0.55	−1.17 to 0.07	.08

“Il pensatore” – August Rodin

Grazie per l'attenzione

camilla.lisanti@cro.it