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Research Article

FAtigue In Radiotherapy and Acupuncture (FAIR-AC) in Breast and Prostate Cancer Patients: A Multicenter Prospective Randomized Phase II Trial

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Abstract

Purpose: A multicenter randomized study was conducted. Patients with breast cancer (BC) referred to post-operative radiotherapy (RT) and patients diagnosed with prostate cancer (PC) referred to radical or post-operative RT were enrolled to evaluate the efficacy of Acupuncture (A) in terms of fatigue (F). **Methods:** 220 patients were recruited and randomized between Arm 1: RT alone, and Arm 2: RT + A. F was assessed with a validated questionnaire (Brief Fatigue Inventory). F was assessed at the beginning of RT treatment, during RT and at follow-up. The questionnaire is composed of 9 items, each represented by a numerical value between 0 and 9 depending on the level of F perceived by the subject. The analysis was conducted both on the individual items and on an overall score that combines all of them. **Results:** 69 BC patients were subjected to RT alone and 63 to RT + A, for PC the numbers in the two arms were 43 and 45 respectively. Analyses were conducted on 183 subjects. In the BC group A offers a significant benefit in items 3, item 6, item 8 and in the overall index. In the PC group the low numbers produce results difficult to comment, especially for items 6 and item 7. The benefit of A appears more pronounced for BC patients with moderate F levels at baseline. **Conclusion:** A may be effective in reducing F for BC patients. No role emerges for PC subjects.

Keywords: Acupuncture; Fatigue; Radiation therapy; Integrative medicine

Introduction

Fatigue (F) has been defined as, "a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functions." [1]. Cancer Related F is very common, experienced by 80% of patients who receive chemotherapy (CT) and/or radiotherapy (RT), as reported in a cross-sectional national survey in US including 1569 patients [2]. Despite its high prevalence and serious adverse effects on quality of life, F is usually underestimated by medical and nursing staff [3]. As for Italy, in 2018 Roila published a cross-sectional study carried out on all patients attending for any reason the 24 participating Italian Oncology Centre, in two non-consecutive days: F was referred by 62.1% of 1394 enrolled patients [4]. RT has been reported to induce F in up to 80% of patients, particularly in those referred to RT for BC and PC [5]. F is frequent in women affected by early BC submitted to adjuvant RT, more severe in patients treated with adjuvant CT before RT [6]. In 186 irradiated BC patients, longitudinal analysis suggests significant cumulative increase in self-reported F severity, on a weekly basis. Overall, the average magnitudes of increase in F score are relatively modest [7]. In BC RT fractionation seems important: BC patients treated with hypo fractionated schedule show less F than those irradiated with conventional schedule [8]. In 97 advanced PC patients treated with Intensity Modulated RT combined with hormonal therapy, F was recently shown to affect severely the quality of life, especially in biologically aggressive disease [9]. In a recent study on 681 patients undergoing RT for non-metastatic PC, F was more frequent and severe in younger patients and in those submitted to androgen deprivation therapy before irradiation [10]. Non pharmacological interventions seem beneficial in F: in a meta-analysis of 113 studies including 11,525 patients, non-pharmacological treatment, specifically exercise and psychological interventions, improved F, while pharmacological interventions did not [11]. The role of Acupuncture (A) for treatment of F is controversial. Meta-analysis and reviews did not succeed in reaching a definite conclusion about the effectiveness of A on F [12-14]. More recently, a meta-analysis by Zhang [15] stated that "Acupuncture is effective for F management and should be recommended as a beneficial alternative therapy for F patients, particularly for BC patients and those currently undergoing anti-cancer treatment". According to a recent review, even Acupressure, that is the pressure of acupoints, appears to affect significant improvements, on the order of 30% to 40% in F [16]. In a pragmatic randomized controlled trial enrolling 302 BC patients experiencing persistent F of at least moderate level, 246 were randomly assigned to A and 75 to standard care. A resulted an effective intervention for managing the symptom of F and improving patients' quality of life [17]. A is reported to be able to reduce some RT side-effect, mainly xerostomia and nausea, but innovative trial designs are demanded in order to demonstrate significant improvements [18]. In a pilot trial comparing verum (i.e. "true") A and sham (i.e. "ineffective") A in 27 BC patients submitted to RT, verum A showed more active but this finding was not statistically significant, due to the small sample investigated [19]. A prospective clinical phase II trial on 74 patients treated with RT in various anatomical regions receiving sham A versus verum A was recently planned [20], but no results have been published to date.

Evaluation of FATIGUE in Traditional Chinese Medicine

Nearly 70 types of symptoms were recorded in the chapter on 'fatigue syndrome' in *Zhubing Yuanhou Lun*, a famous tract about the aetiology and symptoms of disease written during the Sui Dynasty. The symptoms can be categorized into two groups: somatic symptoms including fatigue, a somatic sense of heaviness, cold knees, puffiness, headaches, somatic pain (joint pain and muscle pain) and psychological symptoms, such as depression,

anxiety, restlessness, etc. For an explanation of Traditional Chinese Medicine (TCM), the ultimate reasons for the symptoms described earlier are induced by deficiencies in five organs (including *qi*, blood, *yin* and *yang* deficiencies) caused by the invasion of an exogenous pathogen (i.e. CT and RT), excessive physical strain (manual labour, mental labour and sexual intercourse), abnormal emotional states (elation, anger, worry, anxiety, sorrow, fear and terror) or an improper diet [21].

Characteristics of Chinese semeiotics

A is the perception of small premonitory signs (tics, spasms, functional pains, skin dyschromia) that are elements often neglected by clinical observation, not considered due to lack of coding of the same; but they represent an objective signal of dysregulation of the physiological state of health.

Semiotics:

- It is the auscultation of 28 specific characters of the sphygmic wave (pulsology).

- It is the careful examination of more than 100 characters of the tongue (morphology, induite, examination of the colour and thickness of the same, sublingual veins).

And even for the skin colour, any alterations are taken into great account when it comes to cancer patients.

Pulse diagnosis gives information on:

- The state of balance of the body as a whole, i.e. the state of the Qi, Blood, Yin and Yang
- The state of individual Organs (esp. Yin Organs)

In TCM doctors feel the pulse and note the rate. They discern width or amplitude, length, how close it is to the surface, how deep and close to the bone, the strength and the quality.

Three area of the Pulse (Figure1):

1. Inch or Cun: Distal or Front (at wrist crease)

2. Bar or Guan: Middle (just medial to radial styloid process)

3. Cubit or Chi: Proximal or Rear

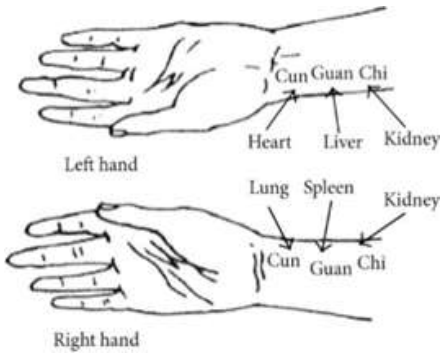

Figure 1

In Chinese semiotics the state of depth of the pulses is analyzed:

Three Levels of the Pulse

Superficial: State of Qi and Yang Organs in general

Middle: State of Blood

Deep: State of Yin and Yin Organs

and also

Superficial: Condition of the Exterior or of the Upper Burner

Middle: Stomach and Spleen diseases

Deep: Interior diseases, esp. Liver and Kidneys

The most frequently encountered pulses in case of cancer are:

1. **CHOPPY, HESITANT PULSE:** caused by consumption of essence, Blood Xu, Stagnation of Qi, Blood Stagnation, Phlegm or food stagnation.

2. **TENSE PULSE:** caused by the contraction of tense vessels resulting from the conflict between cold and healthy Qi and the obstruction of Yang Qi**.** Indicates the location of the tumour depending on the pulse (organ) of reference.

3. **FINE AND WEAK PULSE:** indicates physiological energy deficit (ZHENG QI)

4. **CANTED PULSE:** indicates an imbalance between the right and left pulse, therefore between energy and blood.

Tongue diagnosis gives information by the analysis of the colour, shape and size and coating:

Tongue body color

- This shows the circulation of Qi and blood.
- i.e. A very pale tongue may be a lack of Qi like in chronic fatigue or lack of blood like in anaemia. A purple tongue may indicate chronic pain or poor blood circulation.

Tongue shape and size

- i.e. The tongue should fit in the mouth without swelling and pressing into the teeth. We often see teeth mark indentations in the sides of the tongue which tells us there is digestive system weakness.

Tongue coating thickness and distribution

- i.e. A thick white tongue coating can mean retention of fluids in the body or a build-up of pathogens such as yeast/candida. Alternatively, no tongue coating or a peeled coating can show a lack of fluids or what we call "yin deficiency" which is often seen in menopause.

Color of tongue coating

- i.e. A yellow coating can show a buildup of heat in the body or in a specific organ. Too much heat in the liver area can sometimes mean liver disease or alcoholism.

Tongue moisture

- The tongue should not be overly wet or too dry.

Tongue papules or cracks

- The tongue should be free of purple spots, red dots, or little cracks.

For this study, we chose to examine the characteristics of specific types of pulse and tongue (Table 1,2) in relation to the specificity of the disease (cancer) and the treatment to which the patient is subjected (RT). We compared the characteristics of the pulse and tongue at the first A session with those examined at the last session.

Cun and Guan of right pulse (to analyse the yang ming)	Week Tense Hesitant
Chi of the right and left pulse (to analyse right and left kidney and adrenals)	Week Normal Canted

Table 1

Tongue patina	Absent White Yellow
Body of the tongue	Festooned Thin Swollen
Tongue color	Deep red Pale red Purplish

Table 2

Items for fatigue treatment

The following five items are universally accepted and treatment based upon them can often be clinically effective on fatigue [22].

1.Qi-deficiency of the spleen, characterized by lassitude of the limbs, poor appetite, a pale tongue with white coating and a thready pulse.

In cases of Qi deficiency, there may be no physical abnormality, but the body lacks sufficient energy to perform various functions. In addition to fatigue, the patient has a weak pulse, pale tongue, bright pale face and, possibly, shortness of breath and poor appetite, depending on the organs involved.

Most Qi tonics boost energy by improving the function of the lungs, spleen, and kidneys

A therapy is administered to bring energy to deficient organ. Points are selected that tonify the vital substances, since a deficiency of one or more of them is usually the underlying cause of fatigue (Table 3).

2. Incoordination between the liver and spleen, characterized by mental depression, sighing, fatigue, decreased food intake, abdominal distention, a pale tongue with a white coating and a strong pulse.

3. Blood stasis due to Qi deficiency, characterized by poor spirit, lassitude, somatic pain, insomnia, a pale dim tongue with a white coating and unsmooth feeble pulse.

In cases of blood deficiency, there is insufficient blood to nourish the organs and tissues of the body. In mild cases, the blood count may be within the normal range, while more severe cases are diagnosed as anaemia, which can occur as a result of decreased bone marrow function, vitamin or iron deficiency, general malnutrition, blood

loss from excessive menstrual flow or surgery, or an abnormal destruction of red blood cells from e.i. CT and RT.

In traditional Chinese medicine, anaemia is associated with a deficiency of vital substances in the heart, liver, spleen, and kidneys.

One of the important A point for anaemia is Stomach 36 and it is chosen to improves the assimilation of nutrients from food, aiding in the production of new blood cells.

4. Yin-deficiency of the liver and kidney, characterized by weakness, forgetfulness and insomnia, and soreness and weakness of the waist and knee joints, tinnitus, dry throat and mouth, dysphoria with feverish sensations in the chest, palms and soles, night sweating, a red tongue with little coating a thready-rapid pulse.

5. Yang-deficiency of the spleen and kidney, characterized by cold limbs, listlessness, cold and pain in the waist and knee joints, a pale tongue with a white coating and a deep-thready pulse [23].

Acupoint	Chinese name	Location/Depht of insertion	Functions
Stomach 36 (ST 36)	Zusanli	Below the knee, 3 cun inferior to the inferior line of patella, one fingheer-breadth lateral to the anterior crest of the tibia/ perpendicular insertion1to 1.5 cun	-Harmonises Stomach -Fortifies the Spleen and resolves dampness -Support the correct Qi and fosters the original Qi -Tonifies Qi and nourishes blood and yin -Clears fire and calm the spirit -Activates the channel and alleviates pain -Revives the yang and restors consciusness
Renmai 6 (Ren-6)	Qihai	On the midline of the lower abdomen, 1.5 cun inferior to the umbilicus and 3.5 cun superior to the pubic symphysis/ perpendicular insertion 0.8to 1.5 cun	-Foster original Qi -Tonifdies Qi -Tonifies the Kidneys and fortifies yang -Rescues collapse of yang -Regulates qi and harmonises blood
Renmai 12 (Ren-12)	Zhongwan	On the midline of the abdomen, 4 cun above the umbilicus and midway between the umbilicus and the sternocostal angle/ perpendicular insertion 0.8 to 1.5 cun	-Harmonises the middle jiao and descends rebellion -Tonifies the Stomach and fortifies the Spleen -Regulates Qi and alleviates pain
Renmai 17 (Ren-17)	Shanzhong	On the midline of the sternum, in a depression level with the junction of the fourth intercostal space and sternum/ transverse insertion directed superiorly or inferiorly along the channel 0.5 to 1 cun	-Regulates Qi and unbinds the chest -Descends rebellion of the Lung and Stomach -Benefits gathering Qi -Benefits the breast and promotes lactation

Spleen 6 (SP-6)	Sanyinjiao	On the medial side of the lower leg, 3 cun superior to the prominence of the medial malleulus, in a depression close to the medial crest of the tibia/perpendicular or oblique proximal insertion, 1 to 1.5 cun	-Tonifies The Spleen and Stomach -Resolves dampness -Harmonises the Liver and tonifies the Kidney -Harmonises the lower jiao -Calms the spirit -Invigorates blood -Activates the channel and alleviates pain
Lung 9 (LU-9)	Taiyuan	At the wrist joint, in the depression between the radial artery and the tendons of abductor pollicis lungus/perpendicular insertion 0.3 to 0.5 cun, avoiding the radial artery	-Tonifies the Lung and transform phlegm -Promotes the discending function of the Lung -Regulates and Harmonies the one hundred vassels -Activates the channel and alleviates pain
FROM: ***A Manual of*** **ACUPUNCTURE** ***by Peter Deadman and Mazin Al-Khafaji, with Kevin Baker.***			

Table 3: Acupoints.

The meaning of the QI for tradional Chinese Medicine

The most fundamental concept of TMC is that of "Qi," the life force energy that flows through the body. According to TCM, fatigue is related to the quantity and quality of Qi a person is able to maintain. Qi deficiency, then, is the primary cause of fatigue. Qi runs through and around the body via paths called "meridians." Acupoints are located throughout the body, with the majority located along meridians and A is the process of stimulating acupoints by inserting thin metal needles and manipulating them with manual, electrical, or other forms of stimulation.

Interpreting QI in a modern way

The principle on which A treatment is based lies in the rebalancing of energy, Qi, and our body. The nature of Qi can be scientifically interpreted in light of the biochemical mechanisms of extracellular and intracellular communication. Qi flow can be thought to result from signaling/communication processes such as: phosphorylation/dephosphorylation cascades, the guanine binding protein signaling complex (G binding proteins) and involving the production and degradation of cyclic adenosine monophosphate (cAMP), calcium release and sequestration.

Current scientific knowledge indicates that the energy in our body is stored in the form of ATP. The noble part of the nutrients we ingest, after numerous degradation steps, are mainly converted into adenosine triphosphate (ATP), which is precisely the energy unit necessary for the performance of all cellular functions. An ATP molecule consists of adenine, ribose, and three phosphate groups. Energy is released when the terminal phosphate group is broken down from ATP. About 40% of this energy is used by our body to carry out cellular functions. The rest is converted into heat in order to maintain a stable level of body temperature.

Due to the large incidence of F, good clinical research in this field is mandatory: we need to know the actual incidence of Fatigue related to RT to put in place appropriate treatment strategies. As non-pharmacological interventional seem more effective in treating F, A deserves a special attention for RT-related F. Despite its frequency, RT-related F is not currently monitored and treated in Italy, nor recent studies about its actual incidence in Italian pts are available. The aim of our study is to investigate the actual incidence of F in Italian pts treated with RT and assess the activity of A on F. We conducted a multicentre prospective randomized phase II trial to assess actual incidence of F in Italian pts treated with RT for BC and PC and activity of A in prevention and alleviation of F in BC and PC pts treated with RT (by comparison of results in term of incidence and severity of F in Arm 1 and Arm 2).

The FAIR - AC research project was funded by Tuscany Region.

Materials and Methods

We enrolled consecutive pts affected with BC referred for postoperative RT and pts affected with PC referred for definitive

or postoperative RT to three Radiotherapy Centres (Arezzo, Grosseto, Siena), integrated in Area Vasta Sud Est RT Network (AVSERTN): they were evaluated for F at the start of RT and weekly for the duration of RT by administration of a F investigating questionnaire validated for Italian patients (Brief Fatigue Inventory, supplementary material). At the start of RT, patients enrolled were randomized in two groups (ratio 1:1): in Arm 1 they were treated with "standard care", in Arm 2 with "standard care+A". Patients randomized in Arm 2 pts received A weekly during the 4-8week course of RT. Patients' F was evaluated weekly during RT and two and six weeks after the end of RT.

A multicenter management system has been developed, accessible from the Internet to enabled users. In accordance with the EU DGPR on privacy, the data in the DB are completely anonymous. Study participants are coded with a specific system-generated code. The Centres involved, coordinated by the Institute for Cancer Research, Prevention Clinical Network (ISPRO), are 3 in the Tuscany South East area (Hospitals of Arezzo, Siena and Grosseto). Patient inclusion in the two study arms is automatically assigned by the system during recruitment and cannot be changed in any way by researchers and operators. This was done in stages, an implementation in a test environment, then testing and validation by users and managers, and then putting into production and activating modules. Different roles were assigned according to the different tasks of the various operators i.e. recruitment, data entry and paper keeping by the simple operator, monitoring the progress of the study and accessing data for analysis for the statistician, system development, maintenance and troubleshooting for the administrator role. The system manages the recruitment phase with subsequent random assignment to the treatment arm. The study pathway involves a series of steps with corresponding data recording in both paper and digital form. The sequential steps planned for the trial participant are those of Baseline, Start of Treatment, Treatments (as many as in the treatment plan), Last Treatment, Follow up at two weeks, Follow up at six weeks.

Upon completion of registration of one phase, the next phase is "opened" until the study is completed. The WEB registration forms and related sections, follow the structure of the paper questionnaires prepared. There are mandatory fields marked by specific indicator. Logical jumps and fill-in checks are implemented and are signalled to the compiler with red messages immediately below the filled-in field.

The system also implements the management of out-of-study patients for various reasons by means of special flag field and field describing the reason. In this case, the patient's record is locked and taken to the end of the study without the possibility of continuing the recordings. The records are still viewable or editable for possible corrections.

For users in charge of monitoring and processing the data, there is an option to export to excel format.

The interface was developed as a Microsoft Asp.NET CORE MVC 5.0 project.

WEB platform and DB:

OS:	Microsoft Windows server 2014
WEB Server:	Microsoft IIS 8
DB:	Microsoft Sql Server 2012
Framework:	Microsoft .NET CORE 5.0

A total of 220 subjects (132 with BC and 88 with PC) randomly divided into the two study arms were recruited from the three study Centres. For BC 69 patients underwent RT alone and 63 underwent RT + A, for PC the numerosity in the two arms were 43 and 45 respectively. During the study 37 patients (18 Breast, 19 Prostate) were excluded from the database for various reasons (clinical reasons, agophobia, belenophobia, rejection due to lack of willpower). Analyses were then conducted on 183 subjects (114 breast and 69 prostate).

The analysis was conducted on the various levels of F detected by special questionnaire both at enrolment and at the end of treatment (BFI). The questionnaire consists of 9 items each represented by a numerical value ranging from 0 to 9 depending on the level of fatigue perceived by the subject. Analysis was conducted both on the individual items and on an overall score combining them all, Overall score ranging from 0 to 9 being calculated as a simple arithmetic mean of the individual 9 items.

All tables presented were produced using the statistical analysis package SAS version 9.2. The statistical tests performed are t-tests of the mean when the variables involved are quantitative and of the chi-square test for qualitative variables. Statistical significance is set at 95% with p value<0.05.

Results

Descriptive tables are presented on the number of patients enrolled per Centre divided by pathology of interest and assignment arm (Table 4).

	Treatment	Breast	Prostate	Total
AR	standard	10	0	10
AR	standard + acupuncture	10	1	12
GR	standard	36	9	45
GR	standard + acupuncture	41	8	49
SI	standard	11	30	41
SI	standard + acupuncture	6	21	27
	Total	**114**	**69**	**183**

The F level was overall low for both BC and PC patients at basal evaluation.

For BC and PC patients the mean F levels in the two arms at baseline was then compared for each F questionnaire item. These comparisons are not statistically significant, evidence of the fact that, at enrolment, subjects were randomly distributed across the two study arms (Table 5-6).

	Treatment	N	Mean	Test
Item 1	Standard	57	3.72	
	Standard + acup.	57	3.70	0.97
Item 2	Standard	57	3.90	
	Standard + acup.	57	4.10	0.73
Item 3	Standard	57	4.42	
	Standard + acup.	57	4.93	0.40
Item 4	Standard	57	3.30	
	Standard + acup.	57	3.32	0.97
Item 5	Standard	57	3.88	
	Standard + acup.	57	2.93	0.10
Item 6	Standard	57	2.74	
	Standard + acup.	57	3.26	0.39
Item 7	Standard	57	3.05	
	Standard + acup.	57	3.05	0.99
Item 8	Standard	57	2.70	
	Standard + acup.	57	2.35	0.52
Item 9	Standard	57	2.82	
	Standard + acup.	57	2.35	0.41

Table 5: Breast.

	Treatment	N	Mean	Test
Item 1	Standard	39	1.33	
	Standard + acup.	30	2.13	0.19
Item 2	Standard	39	1.36	
	Standard + acup.	30	1.87	0.35
Item 3	Standard	39	1.62	
	Standard + acup.	30	2.37	0.27
Item 4	Standard	39	1.18	
	Standard + acup.	30	1.63	0.42
Item 5	Standard	39	0.85	
	Standard + acup.	30	1.70	0.10
Item 6	Standard	39	0.64	
	Standard + acup.	30	1.07	0.32
Item 7	Standard	39	0.97	
	Standard + acup.	30	1.17	0.70
Item 8	Standard	39	0.64	
	Standard + acup.	30	0.87	0.57
Item 9	Standard	39	1.05	
	Standard + acup.	30	0.90	0.77

Table 6: Prostate.

Table 7 and Table 8 reported the averages of differences in F levels between end of treatment and baseline, for BC and PC respectively. The difference was calculated both on the individual 9 items and on the overall score which takes into account all 9 items of the questionnaire altogether.

	Treatment	N	Mean	Test
Item 1	Standard	53	1.13	
	Standard + acup.	55	0.27	0.11
Item 2	Standard	53	0.87	
	Standard + acup.	55	-0.11	0.08
Item 3	Standard	53	0.64	
	Standard + acup.	55	-0.54	***0.04***
Item 4	Standard	53	0.96	
	Standard + acup.	55	0.29	0.22
Item 5	Standard	53	-0.04	
	Standard + acup.	55	-0.09	0.92

Item 6	Standard	53	0.96	
	Standard + acup.	55	-0.40	***0.01***
Item 7	Standard	53	0.98	
	Standard + acup.	55	-0.02	0.09
Item 8	Standard	53	0.92	
	Standard + acup.	55	-0.10	***0.03***
Item 9	Standard	53	0.92	
	Standard + acup.	55	-0.22	0.09
Overall	Standard	53	0.78	
	Standard + acup.	55	-0.10	***0.04***

Table 7: Breast.

	Treatment	N	Mean	Test
Item 1	Standard	35	1.00	
	Standard + acup.	28	1.57	0.51
Item 2	Standard	35	0.88	
	Standard + acup.	28	1.46	0.50
Item 3	Standard	35	0.63	
	Standard + acup.	28	0.93	0.72
Item 4	Standard	35	0.45	
	Standard + acup.	28	1.64	0.12
Item 5	Standard	35	-0.54	
	Standard + acup.	28	-0.46	0.86
Item 6	Standard	35	-0.11	
	Standard + acup.	28	0.86	***0.04***
Item 7	Standard	35	-0.51	
	Standard + acup.	28	1.21	***0.01***
Item 8	Standard	35	-0.34	
	Standard + acup.	28	0.11	0.16
Item 9	Standard	35	-0.80	
	Standard + acup.	28	-0.18	0.20
Overall	Standard	35	0.07	
	Standard + acup.	28	0.79	0.16

Table 8: Prostate.

Despite the not too high numerosity, for BC patients significant differences emerge indicating a benefit of A in items 3 (indicate her worst level of fatigue during the last 24 hours), 6 (fatigue interfered with her ability to walk), 8 (fatigue interfered with her relationships with other people) and in the overall index.

On the other hand, for PC patients the low numerosity produces counter results that are difficult to comment on, especially for items 6 (lassitude has interfered with his ability to walk) and 7 (lassitude has interfered with his work).

In this regard, tables are presented by restricting the analysis to those subjects who at baseline already had F levels of at least 3 (based on the overall index). For BC (Table 9), significance is reached in items 1 (indicate your level of fatigue at this time), 2 (indicate your usual level of fatigue during the last 24 hours), 3 (indicate your worst level of fatigue during the last 24 hours), 6 (fatigue has interfered with your ability to walk), 8 (fatigue has interfered with your relationships with other people), and 9 (fatigue has interfered with your enjoyment of life), which are many more than previously. The one based on the overall score is also strengthened. For PC, the very small numbers do not allow for considerations.

	Treatment	N	Mean	Test
Item 1	Standard	26	0.85	
	Standard + acup.	32	-0.53	***0.04***
Item 2	Standard	26	0.23	
	Standard + acup.	32	-1.09	***0.03***
Item 3	Standard	26	0.31	
	Standard + acup.	32	-1.47	***0.01***
Item 4	Standard	26	0.11	
	Standard + acup.	32	-0.56	0.35
Item 5	Standard	26	-0.19	
	Standard + acup.	32	-0.81	0.43
Item 6	Standard	26	0.77	
	Standard + acup.	32	-1.47	***0.01***
Item 7	Standard	26	0.08	
	Standard + acup.	32	-0.97	0.21
Item 8	Standard	26	0.88	
	Standard + acup.	32	-0.84	***0.01***
Item 9	Standard	26	0.69	
	Standard + acup.	32	-0.84	***0.04***
Overall	Standard	26	0.41	
	Standard + acup.	32	-0.95	***0.01***

Table 9: Breast.

Focus about Acupuncture

We have 86 A records but 5 were excluded because the subject had had less than 3 sessions (Table 10).

Table 11 and Table 12 present the averages of A sessions by Centre for BC and PC patients, respectively.

Centre	Breast	Prostate	Total
Arezzo	10	1	11
Grosseto	37	8	45
Siena	6	19	25
Total	53	28	81

Table 10.

Centre	N	Mean	Min	Max
Arezzo	10	3.60	3.0	4.0
Grosseto	37	3.65	3.0	6.0
Siena	6	5.00	5.0	5.0

Table 11.

Centre	N	Mean	Min	Max
Arezzo	1	8.00	8.0	8.0
Grosseto	8	6.50	5.0	8.0
Siena	19	5.58	3.0	8.0

Table 12.

Discussion

Our study on F has shown some interesting results both from the point of view of allopathic medicine and in the framework of TCM [24,25].

As far as gender medicine is concerned, we have an evaluation to note; female subjects with BC were more available and present (114) than men (PC) who were enrolled in a number of 69, in line with what is currently standard detection data about the greater presence of the female sex in the trial and research [26]. It should also be remembered that of the 114 women in treatment, 108 have completed their course, even if not all of them have benefited from the homogeneous criterion of the 8 A sessions normally registered in the South East Tuscany Health Area, modifying the standard goal that we could have expected at the complete cycle.

Despite this data, to be explored in a later staging of the study, we can underline that those who carried out only the standard allopathic treatment increased the F rate by 0.78 compared to a positive figure, remission 0.10, of those who practiced A, thus demonstrating a statistically significant figure of one point of difference, thus improving this significant side effect in the oncological field.

At the same time, the data that highlights how the intensity of F is correlated with the improvement of symptoms was highlighted; in fact, when F is more marked, A improves it significantly, demonstrating the incisiveness of this therapy with regard to the acuteness of the symptom.

As far as the reading of the results in terms of energy (Qi) and functional of Chinese medicine is concerned, a substantial difference in the change in the characters of the tongue and pulse was found in a certain number of patients, especially in the arm of the BC. In fact, the unheard yellow of the tongue, usually initially frequently yellow and sticky, an indication of humidity and heat, tended to normalize and at the end of the treatment was often absent, even the body of the tongue turned from bright red to pink.

Regarding the pulse, defined by the literature in the tense-wide and crusty tumor, we found it rather empty and moderate, an indication of lightening of the toxic content with a mutation of the sphygmic wave less preponderant, with less frequent beats and normality on palpation.

Conclusion

Our study, in line with Zhang's meta-analyses, has several points to be further investigated at a later date but at the same time presents a sufficient sample and demonstrates evidence of effectiveness of the use of A on cancer-related F, also taking into account the homogeneity of the protocols adopted.

After assessing the substantially equal F values at baseline between the two treatment groups and partly excluding (despite some borderline values) the possible confounding action of some variables of interest for both BC and PC patients, it can be concluded that A may play a beneficial role on reducing F by more than one point for BC while no role seems to emerge for PC subjects. This effect appears more pronounced for BC patients when acting on patients with already at least moderate levels of F.

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Conflict of Interest: The Authors declare that they have no conflicts of interest.

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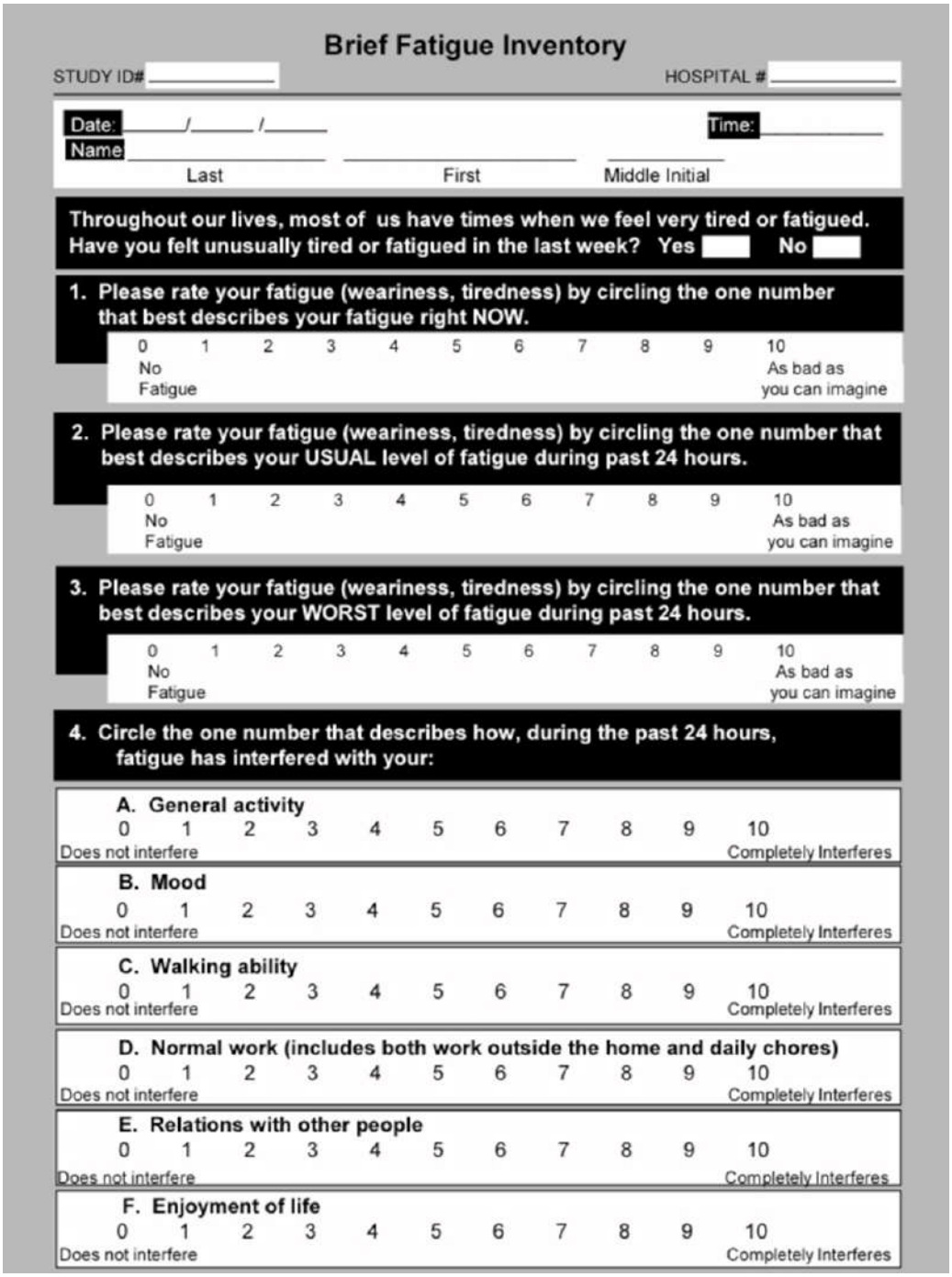
Supplementary Materials

Brief Fatigue Inventory



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name _____ _____ _____

Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — Completely Interferes