	LA GESTIONE DELLA FATIGUE NEL PAZIENTE ONCOLOGICO	Data evidence report
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Introduzione

Pur non esistendo una definizione unica, la *National Comprehensive Cancer Network Fatigue Practice Guidelines* (NCCN) definisce la fatigue cancro correlata (FCC) come "una sensazione soggettiva, stressante, persistente di stanchezza o spossatezza correlata al cancro o al suo trattamento, non proporzionale all'attività eseguita, che interferisce con le abituali attività e che spesso non è alleviata dal sonno o dal riposo" (Fatigoni, Fumi, Roila, 2015)[1].

La fatigue è uno dei sintomi più comunemente riferiti dai pazienti affetti da neoplasia, in passato è stata poco riconosciuta dagli oncologi e raramente valutata o trattata in modo sistematico. Sono stati condotti pochi studi sulla fatigue, e sia la mancanza di ricerca empirica sia la complessità della condizione hanno contribuito ad un senso di nichilismo terapeutico.

Soprattutto in passato, questo nichilismo determinava la riluttanza dei pazienti a lamentarsi della fatigue, che era considerata un sintomo da "sopportare" o un inevitabile effetto collaterale della malattia o del suo trattamento. Solo negli ultimi dieci anni viene considerata un problema significativo (Lesage e Portenoy, 2002)[2].

Secondo Goedendorp et al. (2010)[3], la prevalenza della fatigue correlata al cancro oscilla dal 25% al 75%; diversi studi hanno riportato anche una prevalenza > 90%.

Cramp e Byron (2012)[4] affermano che la FCC ha un profondo effetto su tutta la persona coinvolgendo la sfera fisica, emotiva e mentale, e può persistere per mesi o addirittura anni dopo il completamento del trattamento.

La fatigue impatta in maniera importante sulla qualità di vita del paziente e in particolar modo sulla capacità di lavorare, sulla possibilità di vivere la quotidianità e sulla vita sessuale con conseguenze sociali ed economiche devastanti (Stone et al., 2000)[5].

Nonostante la prevalenza e l'impatto della fatigue legata al cancro, l'eziologia (Figura 1) deve essere ancora pienamente stabilita anche se un certo numero di cause sono state suggerite, come l'effetto del tumore e il trattamento del cancro, le patologie concomitanti incluse anemia, ipotiroidismo, citochine e disturbi del sonno, fattori psicologici come ansia e depressione, e perdita dello stato funzionale (disturbi della memoria, incapacità di concentrarsi, disperazione, aspettative di risultato negativo, capacità di sostenere relazioni con le loro famiglie, capacità di impegnarsi nella vita sociale).

Inoltre la causa della fatigue può variare da individuo a individuo, rendendo difficile sviluppare trattamenti efficaci e, molto probabilmente, impossibile sviluppare un efficace intervento mirato ad un unico meccanismo patopsicologico o patofisiologico che fornirà sollievo per la maggior parte dei pazienti affetti da cancro (Mustian et al., 2007)[6].

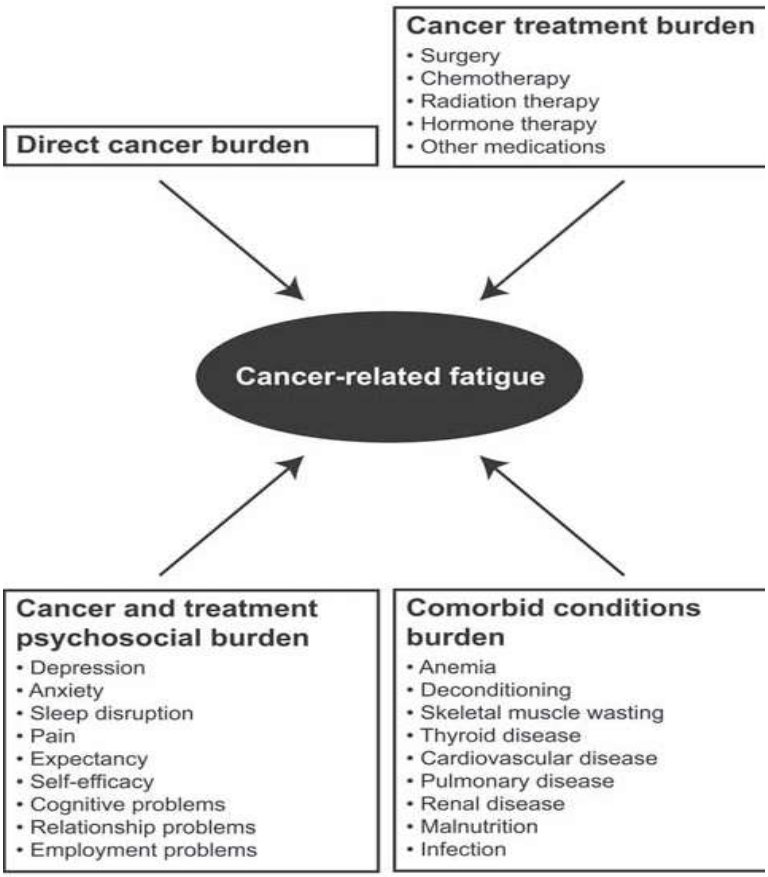

Figura 1 – Eziologia fatigue cancro correlata.

Gli interventi per la gestione della FCC sono limitati sia per il numero che per la validità di prove a sostegno della loro efficacia. L'approccio più efficace per la gestione di qualsiasi sintomo è identificando la causa del sintomo, se può essere identificata, e correggerla, se può essere corretta.

Nelle *National Comprehensive Cancer Network Fatigue Practice Guidelines*, sono identificati sette fattori che contribuiscono alla fatigue cancro correlata: il dolore, la sofferenza emotiva, i disturbi del sonno, l'anemia, le carenze nutrizionali, l' ipotonia muscolare e le comorbidità.

La raccomandazione del panel di esperti è che questi fattori debbano essere valutati e trattati come primo approccio nella gestione del sintomo, sebbene essi possano non essere la causa primaria della fatigue dell'individuo (Mock, 2004)[7] suggerendo un trattamento aggiuntivo a seconda dello stato clinico del paziente (Figura 2): interventi farmacologici e non farmacologici (interventi psicosociali, l'esercizio fisico e una serie di altri interventi integrativi) per la gestione efficace della fatigue cancro correlata (Cramp, Byron, 2012)[4].

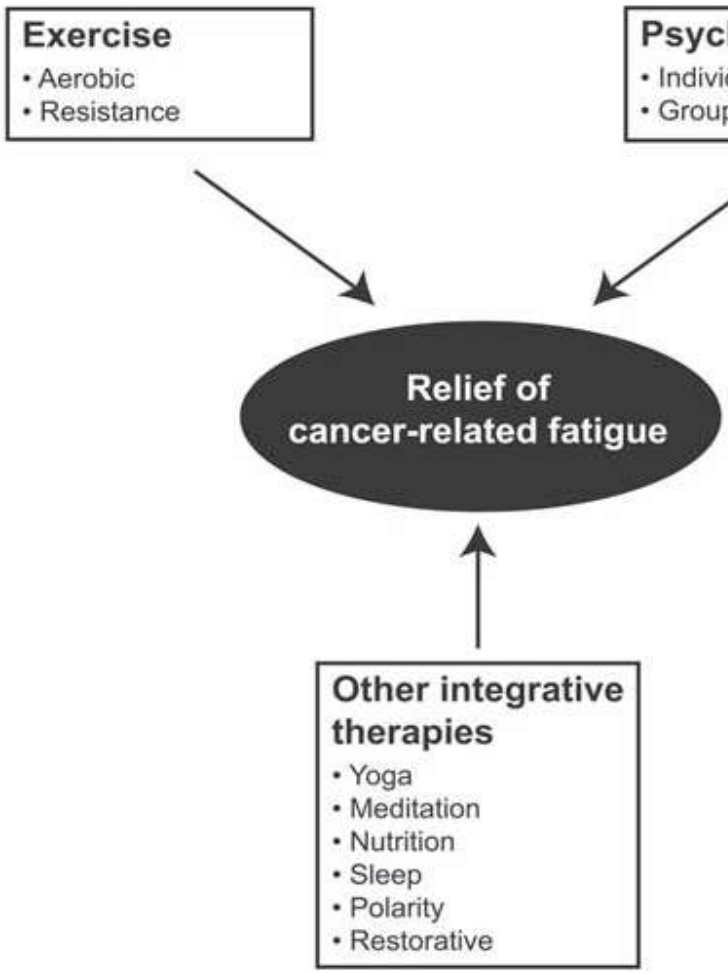

Figura 2 – Interventi per la gestione della fatigue cancro correlata.

Scopo

Lo scopo di questa revisione della letteratura è di poter suggerire, ai pazienti affetti da cancro, interventi non farmacologici che contribuiscano a ridurre la fatigue, portando alla luce un problema spesso sottostimato e che ha, invece, un considerevole impatto sulla qualità di vita del paziente.

Obiettivo dello studio

Valutare l'efficacia dei trattamenti non farmacologici nella riduzione della fatigue cancro correlata nel paziente oncologico.

Criteri di inclusione

Studi di ricerca sperimentali o osservazionali analitici con campione di pazienti con età superiore ai 16 anni affetti da tumore senza selezione di patologia d'organo, durante e dopo trattamento antiblastico in regime di ricovero ospedaliero o a domicilio (*follow up*).

Ricerca in letteratura

La ricerca della letteratura è stata condotta su diversi database: Medline (termini MeSH), Nursing premium, Trip *database*, Knowledge Translation, British Medical Journal, Cochrane Library.

La Tabella 1 mostra le banche dati in cui sono stati selezionati gli studi.

I limiti di ricerca posti sono stati: disponibilità del *free full text* e studi in lingua italiana ed inglese.

Parole chiave: "cancer fatigue nursing", "neoplasm", "fatigue", "exercise", "oncologic nursing", "quality of life", "intervention", "nonpharmacological nursing interventions", "management cancer related fatigue", "cancer related fatigue".

Banca dati	**Stringa di ricerca/limiti**	**N. articoli reperiti**	**N. articoli selezionati**	**Estremi articoli**
Medline	("cancer fatigue nursing")/review/5 anni/humans	66	3	Effects of aerobic exercise on cancer-related fatigue: a meta-analysis of randomized controlled trials. Tian L, Lu HJ, Lin L, Hu Y. Support Care Cancer. 2015 Oct 19. [Epub ahead of print].
				Supervised exercise reduces cancer-related fatigue: a systematic review. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. J Physiother. 2015 Jan;61(1):3-9. Doi: 10.1016/j.jphys.2014.08.019. Epub 2014 Dec 13.
				Exercise for the management of cancer-related fatigue in adults. Cramp F, Byron-Daniel J. Cochrane Database Syst Rev. 2012 Nov 14;11:CD006145. doi: 10.1002/14651858.CD006145.pub3. Review.
Medline	(("Neoplasms"[Mesh]) AND "Fatigue"[Mesh]) AND "Exercise"[Mesh]/5 anni	125	1	Effect of exercise on cancer-related fatigue: a meta-analysis. Tomlinson D, Diorio C, Beyene J, Sung L. Am J Phys Med Rehabil. 2014 Aug;93(8):675-86. doi: 10.1097/PHM.0000000000000083.
Tripdatabase	Oncologic Nursing AND Intervention AND Fatigue/review	41	1	Psychosocial interventions for reducing fatigue during cancer treatment in adults. Martine Margaretha Goedendorp, Marieke FM Gielissen, Constantijn AHHVM Verhagen, Gijs Bleijenberg Cochrane Database of Systematic Reviews 2009.

Tabella 1 – Revisione della letteratura.

Tabella 2 - Tabella di analisi degli studi selezionati

Autore, anno	Popolazione	Intervento /Fattore	Comparazione (se applicabile)	Outcome	Disegno	Conclusioni	Commenti (bias)
Tian, 2015	Adul patients (>18 Years) who were diagnosed with any type of cancer, regardless of gender, tumor stage, and type of cancer tretment. 26 studies with a total of 2830 partecipants	Supervised aerobic exercise, exercise for 20-30 min/ session, exercise three times/week, exercise for 50 min/session, exercise two sessions/week, 8 weeks of exercise	Standard/ usual care or no exercise	The pourpose of this study is to compare the effects of aerobic exercise on CRF with the standard of care. Trials regarding fatigue as a primary or secondary outcam and containing fatigue scores that could be extracted were included	Meta-analysis of RCT	Exercise should be considered as a part of the cancer care standards to mitigate the effects of CRF, expecially in adult breast and nasopharyngeal cancer patient who have completed adyuvant therapy. From this study supervised aerobic exercise, exercise for 20-30 min/ session, or exercise three times/week had a small effect on CRF. Exercise for 50 min/session and exercise two sessions/week had a significant effect, and 8 weeks of exercise had a moderate effect. Differenza di medie: -0,22 (IC95% -0,39; -0,04) Eterogeneità 78%	The large number of breast cancer patient limits the generalizzability to other type of cancer patient. 10 of the included studies had a sample size smaller than 30. The factors of NCCN panel didn't report in this studies, despite these factors influence about fatigue. Scale utilizzate: FACT-F, BFI, R-PFS. For the authors, BFI and R-PFS are more appropriately used in assessing CRF of the breast and colorectal cancer patient
Meneses-Echaveza, 2014	People diagnosed with any type of cancer, without restriction to a particular stage of diagnosis or treatment. Participants may have received active treatment regardless of therapeutic approach (eg, chemotherapy, radiotherapy). 11 studies and 1530 partecipants	The experimental intervention was supervised physical activity. Physical activity was considered as any body movement causing an increase in energy expenditure, and involving a planned or structured movement of the body performed in a systematic manner in terms of frequency, intensity, and duration and is designed to maintain or enhance	The control intervention was sham or conventional care. Physical activity interventions such as aerobic, resistance and/or stretching training were included. All interventions had to be	The primary outcome measure was cancer-related fatigue using the FACT-Fatigue Scale in 55% of the included trials, the EORTC QLQ-C30 in 36% of trials, the PFS in 9% and the SCFS in 9%. Data from all of the included trials were used in the meta- analysis of the primary outcome. The pooled SMD was –1.69 (95% CI –2.99 to –0.39), indicating a moderate reduction in fatigue from supervised physical activity. Due to considerable statistical	Review of RCTs	The overall meta-analysis showed that supervised physical activity has a favourable effect on cancer-related fatigue when compared with conventional care. The final analysis of the results revealed that supervised physical activity interventions are effective in the management of cancer-related fatigue for all types of cancer (SMD = –1.69, 95% CI –2.99 to –0.39). The results of the	Publication bias may have been present, but it was not possible to test for it due to the small number of included studies. Also, heterogeneity was present in most of the meta-analyses. This may be due to the range of sample sizes, the diverse exercise regimens (in terms of length, duration and intensity) evaluated, and the wide variety in outcome measurement tools used in the included studies. No blinding, no Intention to

		health-related outcomes.	supervised by health professionals	heterogeneity ($p < 0.001$, $I2 = 99\%$), this result was calculated using a random-effects model, which was mostly due to a single outlying tr The secondary outcomes were physical and functional wellbeing.		present study are in line with those published by Fong et al42 where physical activity, with or without supervision, was positively associated with body composition, physical functioning and psychological outcomes, including fatigue. Differenza di medie: -1,69 (IC95% -2,99; -0,39) Eterogeneità: 99%	Treat
Cramp, 2012	Adults of any age, regardless of gender, tumour type, tumour stage and type of cancer treatment. Participants may have been actively receiving treatment, be in long-term follow-up or receiving palliative care 56 studies with a total of 4068 partecipants	All types of physical exercise were considered for in-clusion: aerobic exercise, strength training and flexibility exercises. Studies that investigated an exercise programme accompanied by attempts to promote participant engagement were included. In contrast, studies that explored multi-dimensional programmes in which the effects of exercise alone could not be determined were excluded. Studies were also excluded if a specific exercise programme was not described and participants were only given advice or education about the potential benefits of exercise	No exercise or a usual care or an alternative treatment	The outcomes of interest were: 1. patient-reported fatigue measured using reliable and valid assessment tools; 2. exercise maintenance on follow-up; 3. time spent exercising; 4. valid and reliable measures of aerobic capacity; 5. quality of life measures; 6. anxiety; 7. depression; 8. self efficacy (the individual's belief in their own ability to be physically active).	Review of RCTs	Thirty studies provided overall evidence that aerobic exercise is beneficial in the management of fatigue both during and after cancer treatment and should therefore be considered as one com-ponent of a management strategy for fatigue that may include a range of other interventions and education. These findings related specifically to those with solid tumours. Differenza di medie esercizio vs non esercizio: -0,27 (IC95% -0,37; -0,17) Eterogeneità: 33% Differenza di medie in esercizio aerobico vs nessun esercizio: -0,22 (IC95% -034; -010) Eterogeneità: 20%	No blinding, Intention To Treat not clear (Definition of intention-to-treat analysis varied between studies with some studies using this term to describe the inclusion of non-adherent participants in the analysis, whereas others used the term to describe the inclusion of participants who failed to complete the outcome measures or lost contact with the investigators, or both) Hawthorne effect

Tomlison, 2014	72 studies (71 in adults and 1 in children) for 5367 partecipants. The inclusion criteria was three: 1 patient were randomly assigned to an exercise interventio and control intervention, 2 patient were diagnosed with cancer and were in active treatment or follow-up, 3 fatigue was a primary or secondary outcome	Aerobic exercise, resistance exercise/muscle and strengthening, walking, pilates, yoga, stretching exercise, and other (tai chi)	Usual care or a nonexercise intervention	The primary outcome measure was the Fatigue Scire at the end of the intervention or the closest follow-up time point after the end of intervention. Secondary outcomes were depression and sleep disturbance at the end of the intervention period.	Meta-analisis of RCT	The authors found that exercise had a moderate effect in reducing fatigue, depression and slleep disturbance. The benefit of exercise did not differ by tipe of exercise intervention. Howewer the effect of exercise on fatigue reduction may differ by underlyng malignancy tipe, with a stronger effect in solid tumor versus versus haematologic and mixed malignancy tipes. Differenza di medie: -0,45 (IC95% -0,57; -0,32) Eterogeneità: 71%	The study doesn't explain the caratteristic of population. The authors performed a post hoc stratified analys by year of publication and found that exercise had greater effect on fatigue in those studies published in 2009 or later. The reason for this finding is unclear (probably the reason is poorly designed with greater risk for bias)
Goedendorp, 2010	Adult (those aged 16 years and above) cancer patients of either sex, receiving active treatment for cancer, with curative or palliative intention. 27 studies with a total of 3324 partecipants	Psychotherapy, psycho-education and also interventions containing elements such as; education, cognitive restructuring and changing coping strategies. Interventions focusing on behavioural changes were included, for example; behavioural therapy, self-help or self- care. In addition other intervention types such as; support groups, relaxation, energy conservation, or stress management, and interventions combining psychosocial elements with physical activity were included. Both individual and group-focused interventions were included.	Standard care	Fatigue was at least one of the outcome measures. Studies were included when fatigue was measured with a questionnaire specifically designed to evaluate fatigue, or other instruments used by authors to evaluate fatigue.	Review of RCTs	This review showed that the effectiveness of interventions specific for fatigue was significantly higher than interventions not specific for fatigue. To conclude, at present psychosocial interventions specifically for fatigue is the more promising type of intervention for reducing fatigue during cancer treatment. However, there is currently no solid evidence for the effectiveness of interventions not specific for fatigue.	The possibility of bias could be found in the characteristics of the sample. No blinding, no Intention to Treat (only 1) Manca metanalisi

SOMMARIO DELLE EVIDENZE

Sintesi della evidenze

- Moderata evidenza, con elevato rischio di bias, che l'intervento fisico aerobico sia efficace nel ridurre la fatigue nel paziente con cancro ma solo nei tumori solidi (Liv. II).
- Moderata evidenza, con forte presenza di bias, che l'intervento psicosociale (strategie educative, ricostruzione cognitiva, strategie di coping, terapia comportamentale) sia efficace nel ridurre la fatigue (Liv. II).

Livelli delle evidenze

Livello I: Meta-analisi (con omogeneità) di studi sperimentali (ad esempio RCT con randomizzazione nascosta) o uno o più ampi studi sperimentali con intervalli di confidenza limitati.

Livello II: Uno o più piccoli studi randomizzati con intervalli di confidenza più ampi o studi semi - sperimentali (senza randomizzazione).

Livello III: 1. Studi di coorte

2. Studi caso-controllo

3. Studi osservazionali (senza gruppo di controllo).

Livello IV: Opinione di esperti, campo di ricerca fisiologica, o consenso.

Raccomandazioni di buona pratica

- Sono necessari altri studi con un maggiore rigore metodologico. E' necessaria anche una maggior definizione degli interventi da sottoporre a sperimentazione in quanto l'elevata variabilità non consente confronti (forte eterogeneità degli studi nelle metanalisi).

Forza delle raccomandazioni

Grado A: Forte evidenza che ne consiglia fortemente l'applicazione

Grado B: Moderata evidenza che ne consiglia l'applicazione

Grado C: Mancanza di evidenza

Bibliografia

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