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ORIGINAL ARTICLE

The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: a meta-analysis of randomized controlled trials

Ye-min Wang · Bao-zhe Jin · Fang Ai · Chang-hong Duan · Yi-zhong Lu · Ting-fang Dong · Qing-lin Fu

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Abstract
Background Recently, melatonin has been associated with cancer both in vitro and in vivo. However, the value of melatonin in the treatment of cancer remains disputable. Hence, we performed a systematic review of randomized controlled trials (RCTs) of melatonin in solid tumor cancer patients and observed its effect on tumor remission, 1-year survival, and side effects due to radiochemotherapy.
Methods An electronic search was conducted using the databases Pubmed, Medline, EMBASE, Cochrane library, and CNKI, from inception to November 2011. Trials using melatonin as adjunct treatment concurrent with chemotherapy or radiotherapy for cancer were included. Pooled relative risk (RR) for the tumor remission, 1-year survival, and radiochemotherapy-related side effects were calculated using the software Revman 5.0.
Results The search strategy identified 8 eligible RCTs ($n = 761$), all of which studied solid tumor cancers. The dosage of melatonin used in the 8 included RCTs was 20 mg orally, once a day. Melatonin significantly improved the complete and partial remission (16.5 vs. 32.6%; RR = 1.95, 95% CI, 1.49–2.54; $P < 0.00001$) as well as 1-year survival rate (28.4 vs. 52.2%; RR = 1.90; 95% CI, 1.28–2.83; $P = 0.001$), and dramatically decreased radiochemotherapy-related side effects including thrombocytopenia (19.7 vs. 2.2%; RR = 0.13; 95% CI, 0.06–0.28; $P < 0.00001$), neurotoxicity (15.2 vs. 2.5%; RR = 0.19; 95% CI, 0.09–0.40; $P < 0.0001$), and fatigue (49.1 vs. 17.2%; RR = 0.37; 95% CI, 0.28–0.48; $P < 0.00001$). Effects were consistent across different types of cancer. No severe adverse events were reported.
Conclusions Melatonin as an adjuvant therapy for cancer led to substantial improvements in tumor remission, 1-year survival, and alleviation of radiochemotherapy-related side effects.

Keywords Melatonin · Cancer · Meta-analysis · Remission · Survival

Y. Wang · Y. Lu · T. Dong
Department of Pharmacy, The First Affiliated Hospital of Xinxiang Medical University, 88 Jiankang Road, The City of Weihui, Xinxiang, Henan Province, China

B. Jin · F. Ai · C. Duan · Q. Fu (✉)
Department of Surgery, The First Affiliated Hospital of Xinxiang Medical University, 88 Jiankang Road, The City of Weihui, Xinxiang, Henan Province, China
e-mail: drfuql@163.com

Introduction

Melatonin, the main secretory product of the pineal gland, is a direct free radical scavenger, an indirect antioxidant, as well as an important immunomodulatory agent. Recently, both in vitro and in vivo investigations have demonstrated that melatonin also has important oncostatic properties [1, 2]. Studies have verified that melatonin is involved in the prevention of tumor initiation, promotion, and progression. The oncostatic actions of melatonin on neoplastic cells count on its antioxidant, immunostimulating, and apoptotic properties. Melatonin's anticarcinogenic properties include direct inducing of natural killer (NK) cell activity, which enhances immunosurveillance and stimulates cytokine production such as interleukin (IL)-2, IL-6, IL-12, and interferon (IFN)-gamma [3].

Melatonin exerts growth inhibitory effects on breast cancer cell lines in both physiological and pharmacological doses [4]. In hepatic carcinoma, melatonin could inhibit

linoleic acid uptake via activation of MT1 and MT2 receptors, thereby preventing the formation of the mitogenic metabolite 1,3-hydroxyoctadecadienoic acid [5]. Furthermore, there is abundant evidence for the beneficial use of melatonin during chemotherapy [6]. In addition to its direct oncostatic action, melatonin protects hematopoietic precursors from the toxic effect of anticancer chemotherapeutic drugs. Claims include the potential for melatonin to attenuate damage to blood cells from both radiation therapy and chemotherapy [3]. Moreover, melatonin may induce a decline in the frequency of chemotherapy-induced asthenia, stomatitis [7], cardiotoxicity [8], and neurotoxicity [9].

Numerous clinical trials have addressed the impact of melatonin on solid tumors; as yet, however, there is no satisfactory synthesis of the data. We performed a systematic review and meta-analysis of the literature for all randomized controlled trials (RCTs) examining tumor remission, survival at 1 year, and chemoradiotherapy-related side effects that involve the use of melatonin in the treatment of various cancers.

Materials and methods

Study inclusion criteria

(1) Studies included should be random, controlled trials. (2) The research participants should be patients of pathology-confirmed malignancy, regardless of their age, gender, or tumor stage. (3) Trials included should provide details of tumor remission, or survival at 1 year, or chemoradiotherapy-related side effects. (4) Trials included should use melatonin as adjuvant treatment for chemotherapy or radiotherapy.

We excluded animal studies, pharmacokinetic trials, and trials comparing melatonin when combined with other anticancer agents aside from standard chemotherapy regimens.

Search strategy

The literature search, as well as screening of titles, abstracts, and full-text articles, was completed independently by two investigators, according to the inclusion criteria mentioned above. Electronic search was conducted in the database Medline, PubMed, EMBASE, the Cochrane library, and CNKI, from inception to November 2011. The following search terms were used, but not limited to: "melatonin," "pineal hormone," "cancer," "tumor," and "random." Various combinations of the keywords were applied. Moreover, the references of included literature were searched manually, and the *related articles* provided by PubMed were screened.

Data extraction

Information from each study was extracted independently by two investigators, using a standardized data extraction form. Any dispute was solved unanimously via discussion. The literature approved by both investigators could be included in this meta-analysis. If two or more studies have shared research data, then the study that has the largest amount of samples should be included, while others be excluded. General characteristics of the study (author, year of publication, country, study design, sample size), characteristics of the study groups, their comparability on baseline characteristics (age, sex), dose of melatonin, study population (tumor types), intervention, and outcomes (complete or partial tumor remission, survival at 1 year, and chemoradiotherapy-related side effects such as thrombocytopenia, neurotoxicity, and fatigue) were recorded, where available, and double-checked. Where appropriate, an effort was made to complete the data set through communication with the authors.

Quality assessment

Table 1 presents our assessment of trial quality. We determined methods of randomization, allocation concealment, blinding status of patients and assessors, use of placebo, and loss to follow-up. We contacted the study authors to determine items that were inappropriately reported.

Statistical analysis

Statistics was performed in random model, using the software RevMan 5.0.

Results

Search results

The search strategy identified 988 potentially relevant studies, fifteen of which were searched through reference sections of relevant publications or manual search. A flowchart summarizing search results is provided in Fig. 1. Seven hundred and twenty-one publications were excluded since it was clear from the title that they did not fulfill the selection criteria. From the remaining 267 publications, 193 reviews were excluded. Seventy-four articles were read in full, independently by two investigators, to assess their accordance with the predefined inclusion criteria. Forty-eight studies were excluded according to the inclusion criteria, and 26 RCTs on melatonin and cancer were identified. Among them, 18 were excluded due to lack of or inappropriate control. Finally, 8 RCTs [6, 7, 10–15] were included in the meta-analysis.

Table 1 Quality assessment of included studies

Study	Randomization	Allocation concealment	Blinding status	Placebo	Loss to follow-up
Lissoni [7]	Random number table	Yes	Open	No	No
Lissoni [6]	Yes, method unknown	Yes	Open	No	Unknown
Lissoni [10]	Yes, method unknown	Yes	Open	No	Unknown
Yan [11]	Yes, method unknown	Yes	Open	No	0/11 (T/C)
Lissoni [12]	Yes, method unknown	Yes	Open	No	Unknown
Lissoni [13]	Yes, method unknown	Yes	Open	No	Unknown
Lissoni [14]	Yes, method unknown	Yes	Open	No	Unknown
Cerea [15]	Yes, method unknown	Yes	Open	No	Unknown

T/C, melatonin-treated group versus control group

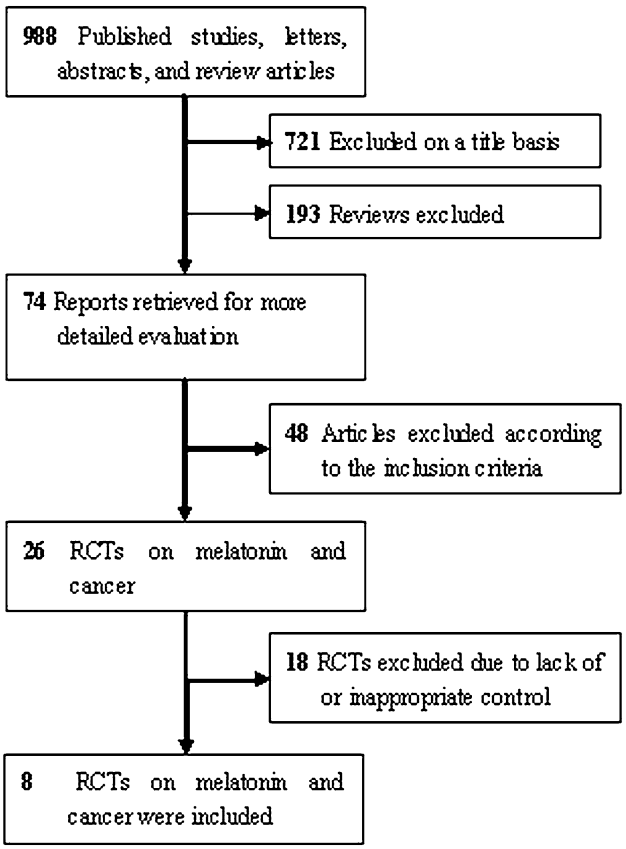

Fig. 1 Flowchart of the systematic review and meta-analysis

Determination of study quality (Table 1) indicates that the studies were of moderate quality, but lacked important methodological techniques shown to potentially prevent bias such as blinding and use of placebo. General reporting of the studies was poor, but contact with the studies' lead authors clarified the missing information. All trials were hospital-funded.

Systematic review

In all, there are 8 RCTs and 761 participants involved in our meta-analysis. These studies were performed from 1996 to 2007. Characteristics of the eligible studies are listed in Table 2. Among the 8 included RCTs, 7 were performed in Italy and 1 was performed in China [11]. Most study participants suffered from metastatic solid malignancy (lung, breast, liver, gastrointestinal tract, head, and neck). Three studies [10, 12, 13] focused solely on metastatic non-small cell lung cancer. Most trials compared the effect of chemotherapy plus melatonin with chemotherapy alone. One Chinese study focused on advanced liver cancer [11] and compared the effect of transcatheter arterial chemoembolization plus melatonin with transcatheter arterial chemoembolization alone. Another study [14] investigated the melatonin therapy in brain glioblastoma and compared the effect of radiotherapy plus melatonin with radiotherapy alone.

Our meta-analysis focused on the efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors. Compared with a recently published meta-analysis [16] that included 21 RCTs, 13 more RCTs were excluded by our study, due to their inappropriate design. These 13 excluded RCTs did not assess the efficacy of melatonin in concurrent chemotherapy or radiotherapy, but focused on its efficacy with concurrent nutritional and supportive care [9, 17–20], hormone therapy [21], or biotherapy (IL-2 [22–25], TNF [25, 26]).

In all of the 8 studies, the dose of melatonin was 20 mg orally, once a day. In most trials, melatonin therapy led to higher tumor remission, better survival at 1 year, and less radiochemotherapy-related side effects. However, one study reported negative results [6].

Meta-analysis

Tumor remission (CR + PR)

All of the 8 included studies reported raw data on completed or partial remission. No significant heterogeneity was found across studies ($I^2 = 0\%$). The random effect model was applied to perform meta-analysis. Pooled data from these 8 studies showed an overall remission rate of 32.6% for melatonin group ($n = 122/374$) and 16.5% for the control group ($n = 64/387$), which was significantly in

Table 2 General characteristics of the included RCTs

Reference	Population	*n* (T/C)	Age range (year)	Interventions	Dosage of melatonin	CR (T/C)	CR + PR (T/C)	Survival at 1 year	Chemoradiotherapy-related side effects
Lissoni [7]	Metastatic solid tumors (lung, breast, gastrointestinal tract, head, and neck)	124/126	60 (39–81)	Chemotherapy + melatonin vs. chemotherapy alone	20 mg/day orally	0/6	42/19	63/29	Thrombocytopenia, 4/31; neurotoxicity, 3/17; fatigue, 33/79
Lissoni [6]	Metastatic solid tumors (lung, breast, and gastrointestinal tract)	39/41	59 (38–76)	Chemotherapy + melatonin vs. chemotherapy alone	20 mg orally in the evening	0/1	12/9	Unknown	Thrombocytopenia, 0/8; neurotoxicity, 0/5; fatigue, 4/19
Lissoni [10]	Metastatic non-small cell lung cancer	49/51	60 (38–81)	Cisplatin + etoposide + melatonin vs. cisplatin + etoposide	20 mg orally in the evening	0/2	17/9	20/10	Thrombocytopenia, 1/7; neurotoxicity, 2/9; fatigue, 4/18
Yan [11]	Advanced primary liver cancer	70/70	52.5 (29–78)	Transcatheter arterial chemoembolization + melatonin vs. transcatheter arterial chemoembolization	20 mg orally in the evening	Unknown	16/9	48/38	Unknown
Lissoni [12]	Metastatic non-small cell lung cancer	34/36	62 (39–80)	Cisplatin + etoposide + melatonin vs. cisplatin + etoposide	20 mg/day orally in the evening	0/1	13/6	15/7	Thrombocytopenia, 0/4; neurotoxicity, 0/5; fatigue, 3/12
Lissoni [13]	Metastatic non-small cell lung cancer	33/35	65 (49–73)	Chemotherapy + melatonin vs. chemotherapy alone	20 mg/day orally in the evening	0/1	13/6	Unknown	Thrombocytopenia 1/7; neurotoxicity, 2/8; fatigue, 4/14
Lissoni [14]	Brain glioblastoma	14/16	50 (32–74)	Radiotherapy + melatonin vs. radiotherapy alone	20 mg/day orally in the evening	Unknown	6/4	6/1	Unknown
Cerea [15]	Metastatic colorectal cancer	14/16	65 (37–82)	Irinotecan + melatonin vs. irinotecan	20 mg/day orally in the evening	Unknown	5/2	Unknown	Diarrhea

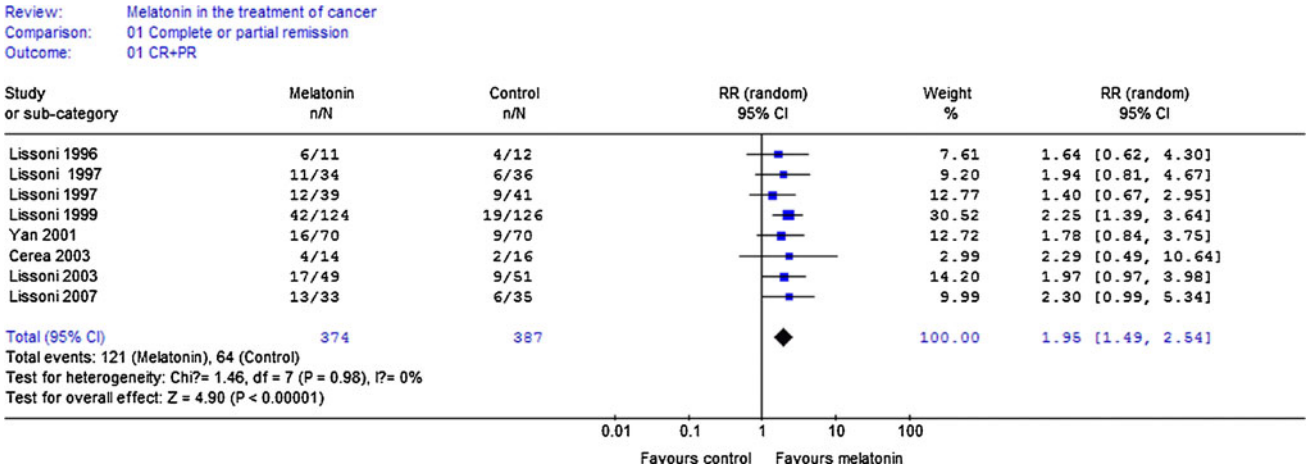

Fig. 2 Meta-analysis on the tumor remission

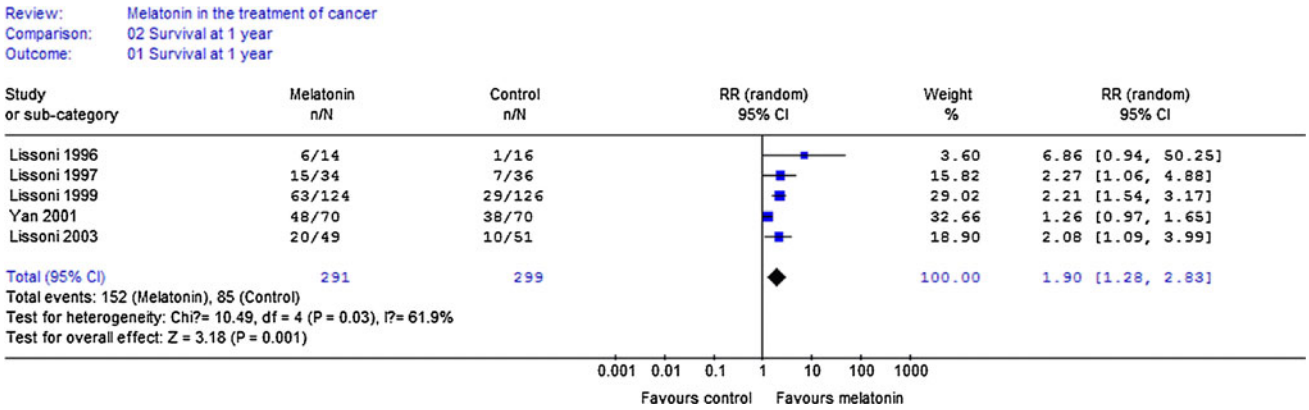

Fig. 3 Meta-analysis on survival at 1 year

favor of melatonin therapy (RR = 1.95; 95% CI, 1.49–2.54; $P < 0.00001$; Fig. 2).

Survival at 1 year

Five studies reported raw data on survival at 1 year. Significant heterogeneity was found across studies ($I^2 = 61.9\%$), and the random effect model was applied to perform meta-analysis. Pooled data from these 5 studies showed an overall 1-year survival rate of 52.2% for melatonin group ($n = 152/291$) and 28.4% for the control group ($n = 85/299$), which was significantly in favor of melatonin therapy (RR = 1.90; 95% CI, 1.28–2.83; $P = 0.001$; Fig. 3).

Radiochemotherapy-related side effects

Thrombocytopenia

Five studies reported raw data on thrombocytopenia due to radiochemotherapy. No significant heterogeneity was found across studies ($I^2 = 0\%$). The random effect model was applied to perform meta-analysis. Pooled data from these 5 studies showed an overall prevalence of thrombocytopenia of 2.2% for melatonin group ($n = 6/279$) and 19.7% for the control group ($n = 57/289$), which was significantly in favor of melatonin therapy (RR = 0.13; 95% CI, 0.06–0.28; $P < 0.00001$; Fig. 4).

Neurotoxicity

Five studies reported raw data on neurotoxicity due to radiochemotherapy. No significant heterogeneity was found across studies ($I^2 = 0\%$). The random effect model was applied to perform meta-analysis. Pooled data from these 5 studies showed an overall prevalence of neurotoxicity of 2.5% for melatonin group ($n = 7/279$) and 15.2% for the control group ($n = 44/289$), which was significantly in favor of melatonin therapy (RR = 0.19; 95% CI, 0.09–0.40; $P < 0.0001$; Fig. 4).

Fatigue

Five studies reported raw data on fatigue due to radiochemotherapy. No significant heterogeneity was found across studies

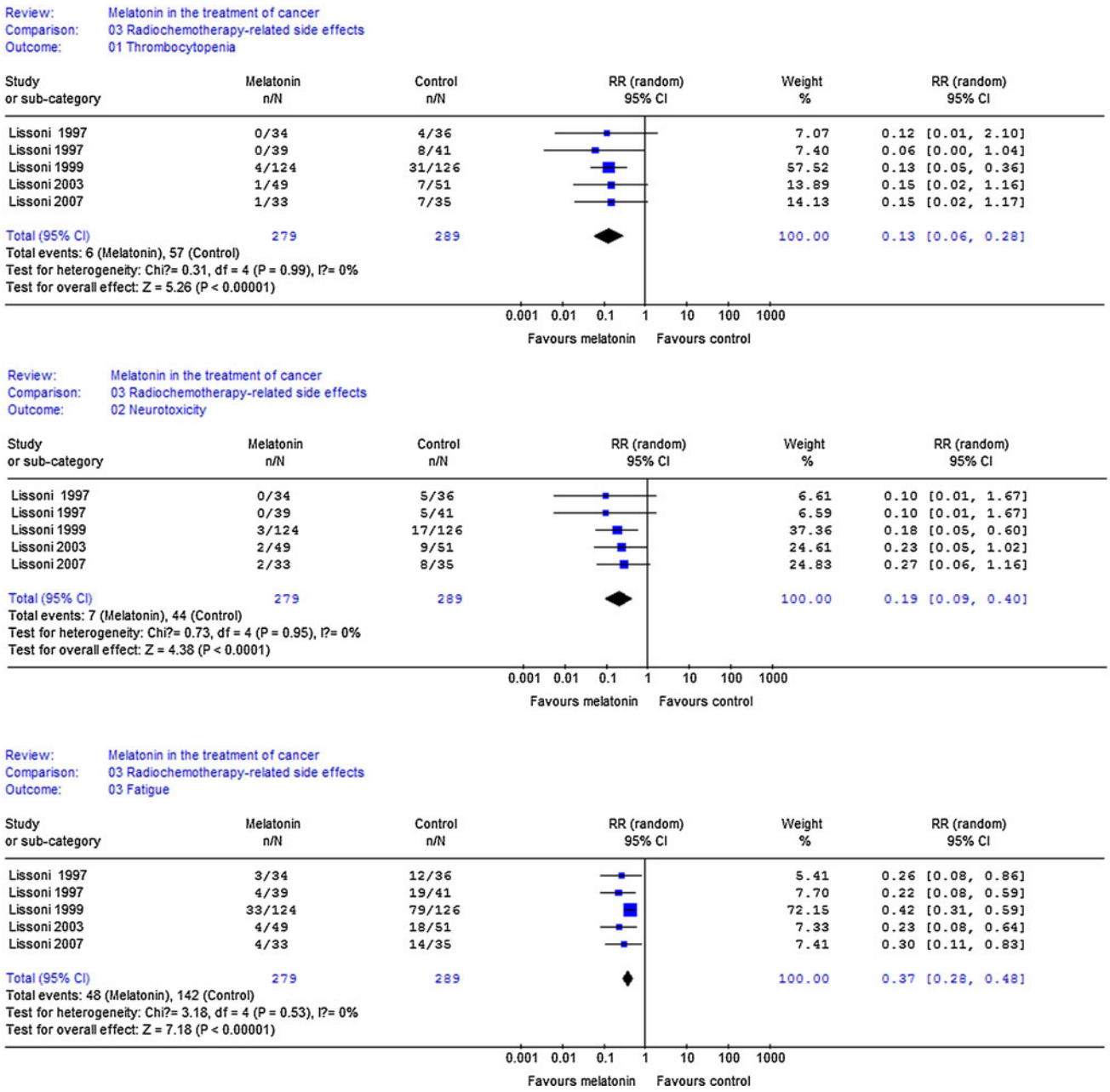

Fig. 4 Meta-analysis on the side effects due to radiochemotherapy

($I^2 = 0\%$). The random effect model was applied to perform meta-analysis. Pooled data from these 5 studies showed an overall prevalence of fatigue of 17.2% for melatonin group ($n = 48/279$) and 49.1% for the control group ($n = 142/289$), which was significantly in favor of melatonin therapy (RR = 0.37; 95% CI, 0.28–0.48; $P < 0.00001$; Fig. 4).

Discussion

Melatonin is a natural antioxidant with immunoenhancing properties. The decline in the biosynthesis of melatonin with age has been suggested as one of the major contributors to immunosenescence and development of neoplastic diseases. Melatonin secretion is also impaired in patients suffering from breast cancer, endometrial cancer, or colorectal cancer [9]. The increased incidence of breast cancer and colorectal cancer seen in nurses and other night-shift workers suggests a possible link between diminished secretion of melatonin and increased exposure to light during nighttime [27]. The physiological surge of melatonin at night is thus considered a "natural restraint" on tumor initiation, promotion, and progression.

In both in vitro and in vivo investigations, melatonin protected healthy cells from radiation-induced and chemotherapeutic drug–induced toxicity due to its antioxidant property. T-helper cells play an important role for protection against malignancy, and melatonin has been shown to enhance T-helper cell response by releasing interleukin-2, interleukin-10, and interferon-γ [3, 28]. Melatonin is effective in suppressing neoplastic growth in a variety of tumors like melanoma [29], breast and prostate cancer, and ovarian [30], and colorectal cancer [3].

Our meta-analysis indicates a consistent effect on tumor remission, 1-year survival, and radiochemotherapy-related side effects of adjunct melatonin in a variety of advanced stage cancers. Melatonin as an adjuvant therapy led to significantly higher tumor remission, better survival at 1 year, and less radiochemotherapy-related side effects including thrombocytopenia, neurotoxicity, and fatigue. In many cases, the cancers that were being treated were refractory to standard therapy and as such more amenable to the adjunct use of an untested and unproven therapy like melatonin. The large effect size and low number of serious adverse events should be of interest to clinicians and patients.

Our study has several strengths. We conducted a systematic search of databases and identified all RCTs available. The electronic search, data extraction, and analysis were done independently and in duplicate. Moreover, we evaluated various study outcomes including tumor remission, 1-year survival, and radiochemotherapy-related side effects. However, the current meta-analysis also has some limitations. The main limitation is that most (6) trials were performed in the same center, while only two studies were performed in other centers. Although the sample sizes of 8 different trials have been pooled, it is still relatively limited. These points may affect the credibility of the results to some extent, and international multicentre RCTs with larger sample size are still needed.

In all of the 8 studies, the dose of melatonin was 20 mg orally, once a day. The 20-mg dosage of melatonin shown to be effective in reducing the risk of cancer is much higher than the 1.5–5 mg regularly used for the treatment of insomnia and jet lag. This raises the question of toxicity and whether or not there are significant side effects at these higher levels of intake. Generally, melatonin is considered relatively safe even at high doses, and the trials included in current study reported no significant side effects. One of the likeliest side effects of melatonin is the tendency to produce sedation or sleepiness in some people. Since melatonin's antioxidant activity is not related to the time of day, to avoid the effect of sedation, it is better to administer melatonin in the evening.

In conclusion, as an adjuvant therapy, melatonin can be beneficial in treating patients suffering from cancer. It is an efficient and cost-effective intervention in cancer treatment and should be of great interest to patients, oncologists, and policy makers. However, more randomized double-blind international multicenter clinical trials with larger sample size are still required to verify its efficacy and safety.

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