

Running Head: Meta-Analysis: Effects of Melatonin in Advanced Cancer Patients with Solid Neoplasms

Melatonin Has Limited Effects on Tumor Regression, Quality of Life, and Treatment Side Effects in Advanced Cancer Patients with Solid Neoplasms

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Abstract

Background Melatonin (MLT) may be a useful therapeutic in the treatment of cancer. Recent meta-analyses, both published in 2012, provided evidence of tumor regression, reduced cancer treatment side effects, and improved patient quality of life (QOL). Notably, over half of the included studies in each meta-analysis came from the Lissoni research group. The present paper is a systematic review and meta-analysis of clinical trials published since 2010 with a focus on MLT's effects on three outcomes: disease progression, cancer treatment side effects and QOL in patients with solid tumors.

Methods An electronic search was conducted using the databases PubMed, EMBASE, and Web of Science. Trials were included if they included MLT and participants with metastatic solid tumors. Data regarding tumor regression, cancer treatment side effects, and QOL were pooled and analyzed using R Studio.

Results Of the 14 studies included, 8 articles were new studies that were compared to six studies were from the Lissoni research group. The other eight studies were new studies published between 2010 and the present. The 14 studies included patients who were given MLT dosages between 10mg and 40 mg every day over the course of the study in addition to the normal cancer treatment therapies. MLT had no effect on patient reported cancer treatment side effects or QOL (Total= 0.05, CI (-2.21 - 2.44); P=0.01, Total= -0.01, CI (-0.58 – 0.56), P=.36). Limited data are provided on tumor regression, making it difficult to statistically analyze on existing data. Additional data are needed to analyze MLT's role in tumor regression.

Conclusions MLT does not improve treatment side effects or QOL in patients with metastatic solid neoplasms.

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Introduction

Cancer is a worldwide public health concern. In 2012, cancer caused 8.2 million deaths globally, making it one of the leading causes of death ^{32, 11}. Likewise, an additional 14.1 million people were newly diagnosed with cancer in 2012, and cancer prevalence is expected to increase further as the population ages ³². Currently, 60% of newly diagnosed cancer cases and 70% of deaths caused by cancer occur in people 65 years and older ³⁰. In America alone, 71 million Americans will be at least 65 years or older by 2025 ³². Therefore, in 2025, the number of newly diagnosed cancer patients is expected to increase 37% globally ^{2, 30, 32}.

With cancer prevalence rising, considerable investment has been made in developing new and improving existing therapy options like cytotoxic chemotherapy, hormonal therapy, immunotherapy, and targeted therapy ²⁷. These therapies, however, do not provide a cure for cancer. In fact, some cancers develop resistance to therapies and threaten the effectiveness of cancer treatment ²⁷. Traditional therapies also reduce patient's quality of life (QOL) by inducing short- and long-term adverse health effects ^{2, 34}. For example, chemotherapy may induce nausea, vomiting, fatigue, and neuropathy. Similarly, patients on hormonal therapy face musculoskeletal discomfort, early-onset of osteoporosis, and increased aortic insufficiency events ²⁷.

Therapeutic success is highly dependent on the timing of cancer detection. The earlier cancer is detected, the more likely the cancer can be successfully treated ¹⁰. Therapeutic success also depends on the number of comorbidities a patient has. On average, patients diagnosed with cancer over the age of 65 experience five comorbidities, and the burden of these co-existing health complications remains relatively unknown ³.

However, having multiple diseases not only negatively impacts a patient's health but also reduces cure and survival rates ^{10, 27, 30}.

Aside from health issues, cancer patients and survivors experience social struggles. For example, cancer survivors often incur significant debt because of the cost of cancer treatment ¹³. Because of this, approximately 64% of cancer survivors will be denied insurance or a loan ³. Cancer patients also experience mental health issues like anxiety, abandonment, and depression, which can linger for the rest of their lives ^{5, 13, 36}.

Because of these complications, literature on adjuvant therapy for cancer treatment is large and growing. A patient is on adjuvant therapy if an additional medication is added to a patient's current treatment regimen ²⁵. The goal of adding an additional medication is to improve the effectiveness and safety of the primary therapy. Current research suggests that MLT may be a helpful adjuvant in cancer treatment. MLT exhibits anticancer properties in a variety of cancer cell lines using varying mechanisms. MLT modulates the cell cycle, induces apoptosis, reduces tumor migration and angiogenesis, limits chemotherapy toxicity, and exhibits anti-proliferative effects through radical oxygen species mediated pathways ^{15, 16, 24, 34, 35}. Melatonin may also be of benefit via improved circadian regulation of physiological processes or because of anxiolytic or antidepressant effects. The aim of this paper is to examine the effect of MLT on tumor progression, side effects of primary tumor treatment, and patients' QOL.

What Is Cancer?

Cancer is the name given to a collection of diseases in which cells exhibit abnormal growth. Common genetic mutations that drive cells towards cancer-like behavior occur in proto-oncogenes, tumor suppressor genes, and DNA repair genes ⁵. Proto-oncogenes are

genes that promote normal cell growth and division. If these genes are either inhibited or overexpressed, cells will grow and survive when they are not supposed to. Tumor suppressor genes slow the rate of cell division preventing cell buildup. Mutations in these genes lead to irregular cell growth. DNA repair genes code for proteins that fix damaged DNA. A mutated DNA repair gene will not correct errors in the DNA, enabling error replication and spread of cancer ⁵. Cancer cells also have the ability to resist cell death, invade tissues of the body, induce development of new blood cells, and evade the immune system ³⁴. With the loss of regulatory mechanisms, cells become immortal.

Proto-oncogenes, tumor suppressor genes, and DNA repair genes are in every cell of the body. Therefore, cancer can start anywhere. Initially, the three mutations above will cause a local cell to proliferate forming masses called tumors. If some of these cells break off the tumor and spread to other tissues of the body via the blood or lymphatic system, the cancer is said to have metastasized ^{5, 25}. It's important to note that not all cancers form tumors. For example, cancer of the blood, or leukemia, does not form tumors ⁵.

Cancer is characterized by tumor growth, metastasis, and disease progression. Terms like "localized, regional, and distant" are used to describe how far the cancer has spread from the position the cancer first appeared ⁵. At the same time, roman numerals between zero and four are used to describe cancer progression ⁵. Stage 0 indicates abnormal cell growth that is not cancerous while stage IV indicates that the cancerous cells have metastasized to multiple areas of the body. The lower the number, the more localized the cancer is. Diagnosing cancer at an early stage is beneficial because treatments are more effective when the cancer is localized ¹⁰. Therefore, stage IV cancer is often described as

incurable because it is harder to treat. In fact, most people who die of cancer, die of metastatic disease ⁵.

How a patient's cancer is treated depends on the type of cancer, tumor size, location in the body, stage, and past medical history ⁵. Based on these factors, a patient's treatment plan can be personalized using one of the following: radiotherapy, chemotherapy, immunotherapy, hormonal therapy, or surgical intervention. Radiotherapy uses large doses of radiation to cure, prevent, or slow the rate of tumor growth ⁵. Chemotherapy uses drugs that have the same effect. Immunotherapy uses the immune system to treat cancer. Specifically, administration of monoclonal antibodies can be used to tag cancer cells ⁵. This tag is then recognized by immune cells and can initiate apoptosis. Immunotherapy can also be used to boost a patient's immune system. In this case, inhibitors of the immune system are turned off, enabling the immune system to operate without limitations. Hormonal therapy is specific for cancers that thrive off hormones. For example, hormone therapy is used for breast and prostate cancer. By blocking certain hormone production pathways, these cancer cells will be unable to replicate and survive ⁵. Finally, surgical intervention entails removal of a localized solid tumor.

Despite meaningful progress, cancer treatment still faces many obstacles. For example, cancer recurrence following remission is common. Cancer originates from stem cells that are difficult to target for treatment. The mutation that enables these cells to self-renew is unknown⁶. Without a marker to target, these cells likely exist after primary treatment. Cancer cells also have drug resistant properties. Specifically, cancer stem cells contain an ATP-binding cassette transporter protein that enables them to flush toxic agents out of the cytoplasm ⁶. This makes anticancer drugs like the ones used in chemotherapy

ineffective. Finally, cancer diagnosis is difficult because patients are oftentimes asymptomatic in the early stages of their disease. Because they are asymptomatic, patients are not treated early, allowing the cancer to spread ⁶. As cancer metastasizes, treatment effectiveness decreases as the surface markers of the target mutates ⁶.

What Is Melatonin?

Melatonin, (MLT) is a multifunctional indoleamine neurotransmitter that is synthesized from the amino acid tryptophan in most cells of the body including the digestive system, skin, retina, and bone marrow ³⁴. The major contributor of systemic MLT in the central nervous system is the pineal gland. Pineal MLT drives an organism's circadian rhythm and is modulated by light, age, gender, and seasons ^{28, 34}. However, circadian regulation is only one of MLT's functions ^{16, 28, 34}. MLT's hydrophobic characteristic enables it to diffuse into adjacent tissues where it initiates immunomodulatory, anti-inflammatory, antioxidant, vasoregulation, and oncostatic activities ³⁴. MLT induces these effects by binding to the G-protein-coupled receptors (GCPR) MT1 and MT2 ^{16, 28, 34}. MLT also interacts with orphan nuclear receptors and molecules found in the cytosol of cells ²⁸. MLT is considered a nutraceutical and is not regulated by the FDA. It has a long shelf-life, is inexpensive to make, and is thought to have few or no adverse effects even at high doses ²⁴.

Melatonin and Cancer: Putative Mechanisms for Beneficial Effects

Mechanisms of Melatonin on Solid Tumors

Research suggests naturally-occurring MLT may have beneficial effects as a cancer preventative and as an adjunct of traditional cancer treatments. MLT achieves these effects through multiple pathways. For example, MLT induces genetic instability in cancer cells by

inhibiting cancer cells' telomerase ³⁴. Telomerase is a protein that protects the ends of a cell's chromosomes. Without it, DNA is shortened each time it is replicated leading to cell death ³⁴. MLT also downregulates p38 MAP kinases, a subgroup of cell behavior mediators involved in cell proliferation, differentiation, death, migration, and invasion. Upregulation of p38 MAP kinase is linked to advance stages of solid tumor cancers ¹⁵. Therefore, when MLT downregulates this pathway, MLT prevents the tumor from metastasizing ^{15, 16}. Finally, MLT blocks substrates from binding to enzymes involved in the calcium/calmodulin (Ca²⁺/CaM) pathway. Without activation of Ca²⁺/CaM pathway, cancer cell proliferation is inhibited. MLT can also induce leakage of Ca²⁺ into cells causing apoptosis ²⁴.

More generally, MLT can interfere with the acetylation and methylation of genes in gene transcription ²⁴. By inducing acetylation of cancer cell genes, the sensitivity of the tumor to the chemotherapy increases, making the chemotherapy more effective. Likewise, MLT can induce methylation of a cancer cell gene, disrupting the cell life cycle and inducing apoptosis. Through these mechanisms and many others demonstrated in Figure 1, MLT may improve the cancer survival rate and tumor response in cancer patients by increasing efficiency of treatment ²⁴.

Effects of Melatonin on Treatment Efficiency and Side Effects

When MLT is taken as an adjuvant with chemotherapy or radiotherapy, treatment side effects like reduction of sleep, depression, and lower health-related QOL are improved ²⁴ (Figure 2). MLT achieves this by increasing the cancer cells' response to primary cancer therapies and re-establishing the circadian rhythm ²⁴. For example, phosphoinositide 3-kinase (PI3K/AKT) plays a role in activating cancer cell proliferation. This mechanism is

accelerated by certain chemotherapy drugs like 5-FU. However, when MLT is taken in combination with this drug, PI3K/AKT signaling is suppressed. This stops cancer cell replication leading to cell death ²⁴. When MLT is paired with radiotherapy, MLT increases arsenic trioxide, a reactive oxygen species and its receptor, Redd1 ¹⁶. Once bound to its receptor, arsenic trioxide can cause cell death ¹⁶. Finally, re-establishing a person's circadian rhythm decreases chemotherapy-induced toxicity on normal cells, ultimately reducing the side effects chemotherapy cancer patient's experience ²⁴. This correlates to the idea that lower secretion of MLT is associated to higher rates of cancer development ^{24, 35}.

The Present Study

While two prior meta-analyses, Seely 2012 and Wang 2012, indicate that MLT has positive effects, there is still some uncertainty whether or not MLT is beneficial in cancer treatment because of lack of multicenter clinical trials ^{29, 35}. This analysis assesses whether recent clinical trials replicate the benefits MLT is suggested to have on QOL and treatment side effects by comparing new data to that published in the Lissoni labs. Replication of the effects on tumor regression is especially important as documented in the previous meta-analyses. Only one of the eight studies in Wang 2012 was not from the Lissoni lab and in Seely 2012, only three of the 21 studies were not from the Lissoni lab. Therefore, this study attempts to answer the following questions by compiling data from a more diverse study pool:

1. Does MLT induce tumor regression in advanced cancer patients with solid neoplasms when used as an adjuvant therapy?

2. Does MLT improve cancer-therapy side effects in advanced cancer patients with solid neoplasms when taken as an adjuvant therapy?
3. Does MLT improve advanced cancer patient QOL when taken in addition to traditional cancer therapies?

Methods

Search Strategy

A systematic literature search of PubMed, Web of Science, and EMBASE was performed using the following keywords: (melatonin AND (Neoplasia OR Neoplasias OR Neoplasm OR Tumors OR Tumor OR Cancer OR Cancers OR "Malignant Neoplasms" OR "Malignant Neoplasm" OR Malignancy OR Malignancies OR "Benign Neoplasms" OR "Benign Neoplasm"))). Only articles published between 2010 and 2018 were included in this meta-analysis in addition to Lissoni papers found in previous meta-analyses. This date range was selected because the two prior meta-analyses on this topic concluded their search in 2010. The initial literature search yielded 551 articles written in English and studying the human population. Of the 551 articles, 36 of the articles looked relevant (Figure 3).

Inclusion and Exclusion Criteria

To be included in this meta-analysis, studies had to have a MLT treatment group, a sample with metastatic solid tumors and clinical intervention. Studies looking at cell lines were not included. The researcher only searched databases accessible to CU students, and the selected articles had to be free. Both randomized control trials and observational study designs were used.

After applying the above stated inclusion criteria, 27 articles were excluded based on title because of duplication, yielding 36 articles to read in full. Of those 36 articles, 22

articles were excluded as follows: 1 study was a case study, 3 were in vivo/in vitro studies, and 19 articles analyzed different interventions than the one of interest.

Overall, 14 studies were kept for analysis. Of these 14 studies, 8 studies were not in the previously published meta-analyses ^{24, 35}. Of these 8 studies, 6 were randomized control trials and the other 2 were clinical trials. Quantitative and qualitative data were extracted from each study regarding the following outcomes: author, year of publication, study sample size, cancer diagnosis, intervention, dosage, study duration, and outcomes like QOL, survival rate, and disease progression.

Data Extraction

Information from each study was extracted independently by one investigator. Any uncertainty was solved by discussion between the investigator and mentor. Defining characteristics of the study like author, year of publication, study design, sample size, baseline and treatment conditions, and outcomes were recorded when available. Table 1 displays a quality assessment of each study. The quality of a study was based on randomization, allocation concealment, blinding status, presence of control, and the number of participants that dropped out of the study.

Table 1 reveals a quality trend based on publication date. The majority of the Lissoni studies published before 2010 lacked double blinding and allocation concealment. These factors increase the risk of bias. Most of the publications after 2010 contain blinding and allocation concealment, which decreases risk for bias. Overall, this meta-analysis contains moderate quality studies.

Systematic Review

This study includes 12 randomized control trials and 2 clinical trials with a total study population of 1,762 participants. The date of publications ranges from 1994 to 2017. All Lissoni studies were performed in Italy. Other studies were performed in Denmark ^{4, 23}, Israel ¹, Thailand ^{26, 31}, United States of America⁷, and Canada ¹⁴. The studies contained participants diagnosed with various types of metastatic solid tumors including non-small-cell-lung cancer, head and neck cancer, breast cancer, and GI cancers. Patients were typically treated with immunotherapy, chemotherapy, or palliative care (Table 2). One study, Bush 2016, focused on MLT's effect on QOL after either a lumpectomy or mastectomy for breast cancer. Another study, Onseng 2017, used an oral gargle MLT solution in patients with oral mucositis. This meta-analysis focused on three outcomes: disease progression, cancer-treatment related side effects, and QOL.

Meta-Analysis

Tumor Regression

Of the 14 included studies, three non-Lissoni studies analyzed disease progression. However, statistical analysis was not performed on these studies because the studies reported different variables making it difficult to cross-analyze. Two of the three studies, Sookprasert 2014 and Del Fabbro 2013, indicated no difference in survival rate between the MLT treatment group and control group. The last study, Vigore 2010, looked specifically at the number of patients who reached disease control versus progressing disease.

A patient exhibits a partial response to treatment if tumor size decreases by 50% and no new growth occurs for a least one-month post-treatment. Disease control is the sum of the number of patients who achieved complete and partial responses. Progressive disease

indicates a patient has 20% new growth during treatment intervention. In this study, 5% of patients showed a partial response to MLT and palliative care while 55% of patients reached a disease stabilization. Therefore, 60% of patients reached disease control during this study. The other 40% of patients had progressive disease despite MLT consumption.

Four of six Lissoni studies analyzed disease progression similar to that of Vigore 2010. However, Lissoni measured the number of patients who achieved partial and complete responses to their cancer therapies. A patient achieves a complete response to treatment if the cancer completely disappears and no other growth occurs for at least one-month post-treatment. The number of partial and complete responses are then summed to create the variable tumor regression. Tumor regression is equivalent to Vigore's disease control variable. In Lissoni's MLT group, 24% of patients showed tumor regression versus only 4% in the control group.

Treatment Side Effects

Of the 14 included studies, 5 non-Lissoni studies analyzed the effects of MLT on treatment-side effects like fatigue, anemia, dermatitis, and oral mucositis. Considerable heterogeneity was found across studies ($I^2 = 73\%$). The random effect model was applied to perform the meta-analysis. Pooled data show an overall rate of treatment side effect presence of 82% while the control showed a treatment side effect occurrence rate of 71%. The data favor the control over melatonin therapy (Total= 0.05, CI (-2.21-2.44); $P=0.01$; Figure 4).

Quality of Life

Four non-Lissoni studies and four Lissoni studies looked at MLT's effects on QOL. No significant heterogeneity was found across studies ($I=6\%$), and the random effect model

was used to run the meta-analysis. Together, the data indicate an overall average QOL measure of 75.88 for the MLT treatment group and 77.225 for the control group, indicating insignificance difference between the two groups (Total= -0.01, CI (-0.58 – 0.56), P=.36; Figure 5).

Discussion

Based on the data from this meta-analysis, MLT does not improve treatment side effects in advanced cancer patients with solid neoplasms. However, the studies looking at MLT's effect on reducing side effects had a high heterogeneity factor indicating that the studies may have been too different to compare MLT's effects. On the other hand, this meta-analysis showed slight favoring towards taking MLT to improve health-related QOL, which is in interest of clinicians and patients despite the insignificance of the results.

Despite differences between the studies, a recent study published in 2018 indicates that the effects of MLT vary with different cancers. Specifically, MLT is more effective in targeting cancer cells that are resistant to chemotherapy ²⁴. Therefore, if MLT is being used in adjuvant to cancer cells that are not resistant to chemotherapy, effects may be limited. Likewise, for MLT to interact with cancer cells most effectively, patients must avoid light exposure at night. Exposure to light after taking MLT reduces MLT interactions with tumor cells and is linked to bigger tumor sizes ²⁴. It is also possible that this meta-analysis saw different results than Najafi's review because the review analyzed cells lines. Cell lines differ greatly from human subjects because cell lines have controlled and homogeneous environments. This is unattainable in cancer patients. Therefore, even if MLT acts on pathways influencing cell replication and apoptosis, the multiple other diseases cancer patients have may limit MLT's abilities.

Meta-Analysis: Effects of Melatonin in Advanced Cancer Patients with Solid Neoplasms

Initially, this meta-analysis hoped to further analyze MLT's effect on disease progression. However, only three new studies looked at disease state, and their outcomes were different than the four Lissoni studies. Specifically, Sookprasert 2014 and Del Fabbreo 2013 only analyzed survival rate rather than complete and partial treatment response and progressive disease or tumor regression. Both studies showed that there was no difference in survival rate between the MLT and control groups. However, it is noteworthy to mention that in Sookprasert 2014, only patients taking MLT were alive 22 months after the study began. Vigore 2010 was the only study that used Lissoni's variables to study MLT's effects on disease state. While the study reported a tumor regression rate in 55% of the patients, the study did not contain a control as MLT was used as a last-resort medication. This differed from Lissoni's population which contained cancer patients receiving chemotherapy, radiation, or immunotherapy. Therefore, to truly know whether or not MLT induces change in cancer progression, we need additional studies.

Finally, the Innamotio 2016 study looked at MLT's effects on treatment effects but was not included in the meta-analysis as this was a secondary outcome and data were not available in the published paper. Similarly, Del Fabbreo 2013 considered MLT's effect on health-related QOL and treatment side effects but reported data as a percentage change from baseline versus the average assessment score and incidence rates of experienced side-effects. This made it difficult to compare the study to the other studies in this meta-analysis.

A strength of this current meta-analysis includes searching three major scientific databases. Likewise, multiple variables were analyzed: cancer treatment side-effects,

patient QOL, and tumor regression. Finally, this meta-analysis contained studies from different research groups unlike previous meta-analyses.

However, this study has limitations. A major limitation of this study is that only one individual completed the search and selection of articles. This raises risk of bias. It is possible that articles were excluded that may have been relevant to this study. Another limitation would be that not all articles looked at all three outcomes. Although the pooled study population is large, the subset populations looking at each variable is much smaller. The current study also has limited generalizability as the population of this study is metastatic, solid cancer patients. Different results may be seen in patients with non-solid cancers or non-terminal cancer. Additional studies are needed to look at the effects of MLT on these cases. Together, these factors may influence the credibility of this study and indicates the need to continue researching MLT's role in cancer treatment in the future.

Overall, using MLT as an adjuvant therapy in patients with solid-neoplasm cancers is unlikely to have a major impact on patients' cancer therapy side effects and health-related QOL. However, more data are needed to confirm these findings and answer whether MLT is associated with tumor regression.

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Figure Captions

Figure 1. Effects of melatonin on different cancer characteristics. Arrows indicate activation. Ts indicate inhibition. Image from Talib (2018).

Figure 2. Mechanisms describing how melatonin improves the efficiency of chemotherapy and radiotherapy and improves cancer therapy side effects. A indicates effects of MLT when used as an adjuvant for chemotherapy. B indicates effects of MLT when used as an adjuvant for radiotherapy. C indicates the effects of MLT alone. Arrows indicate activation. Ts indicate inhibition.

Figure 3. PRISMA flow chart exhibiting selection process used to identify relevant literature for current study.

Figure 4. Meta-analysis on the effect of MLT on treatment side effects experienced by advanced cancer patients with solid neoplasms. Significant heterogeneity was found among studies ($I^2 > 10\%$).

Figure 5. Meta-analysis on MLT's effects on advanced cancer patient's quality of life ($p > 0.05$ indicated insignificant results).

Figures

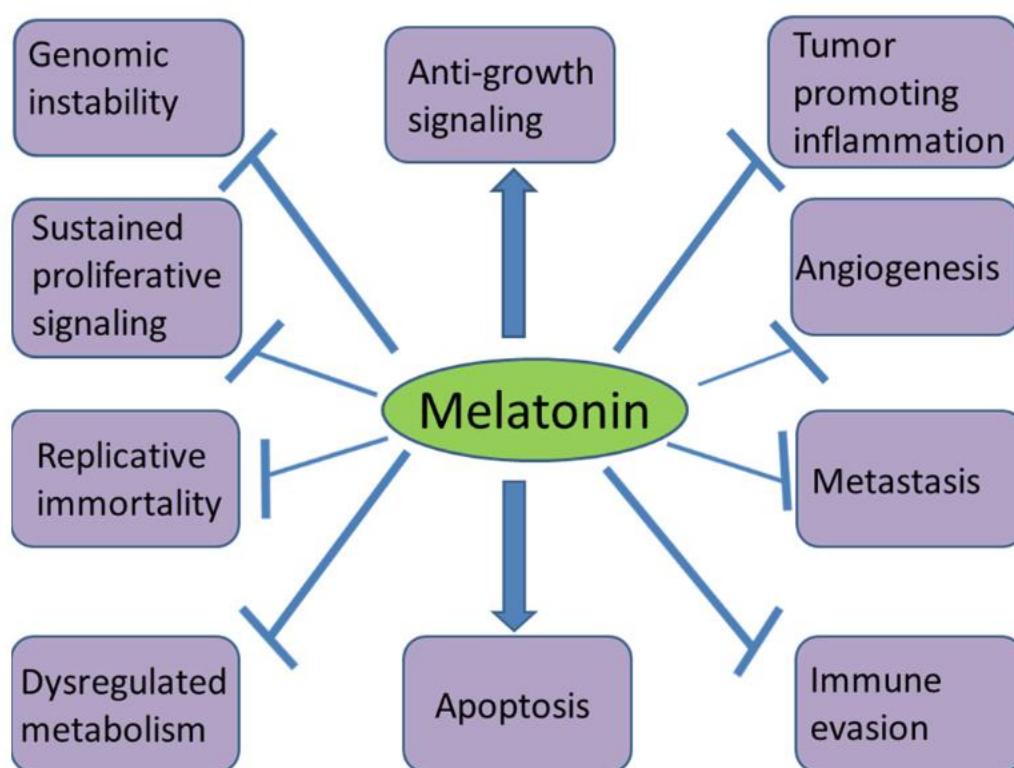


Figure 1.

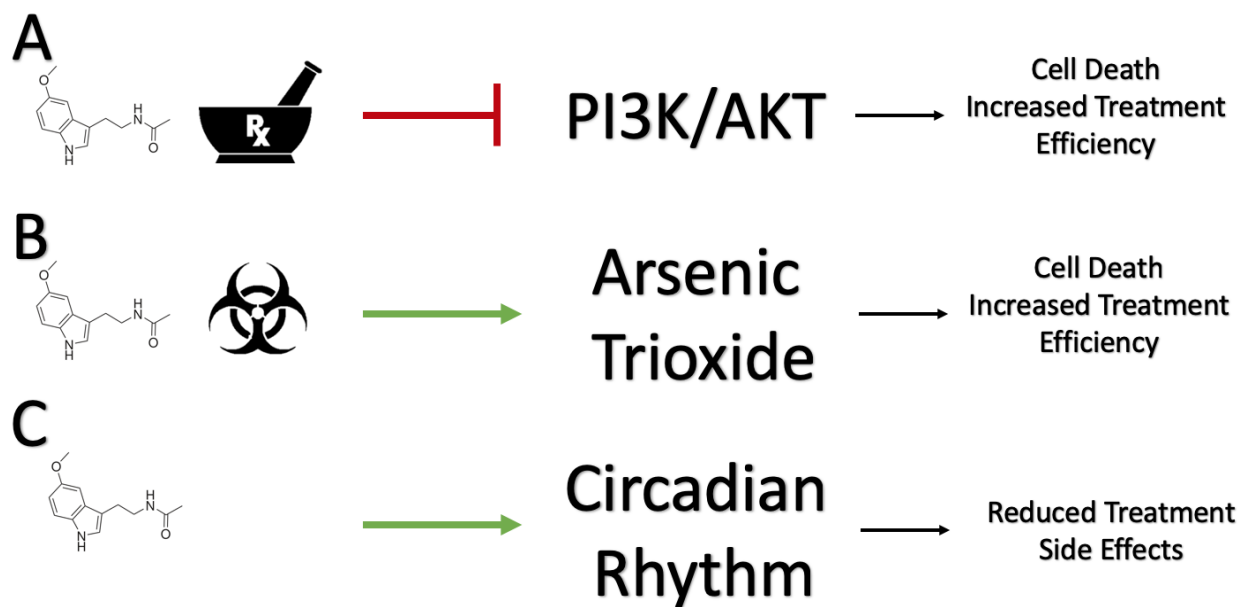


Figure 2.

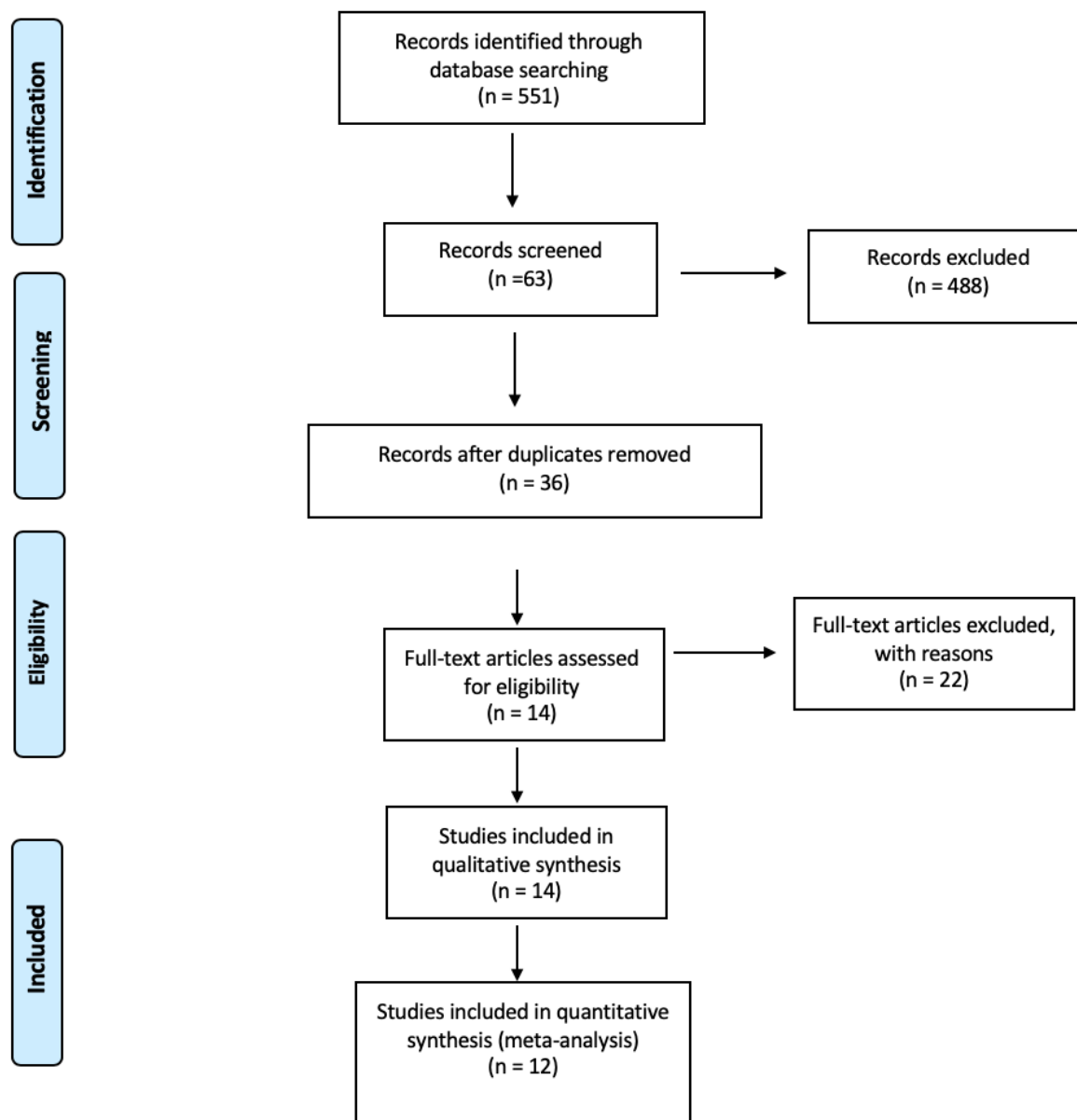


Figure 3.

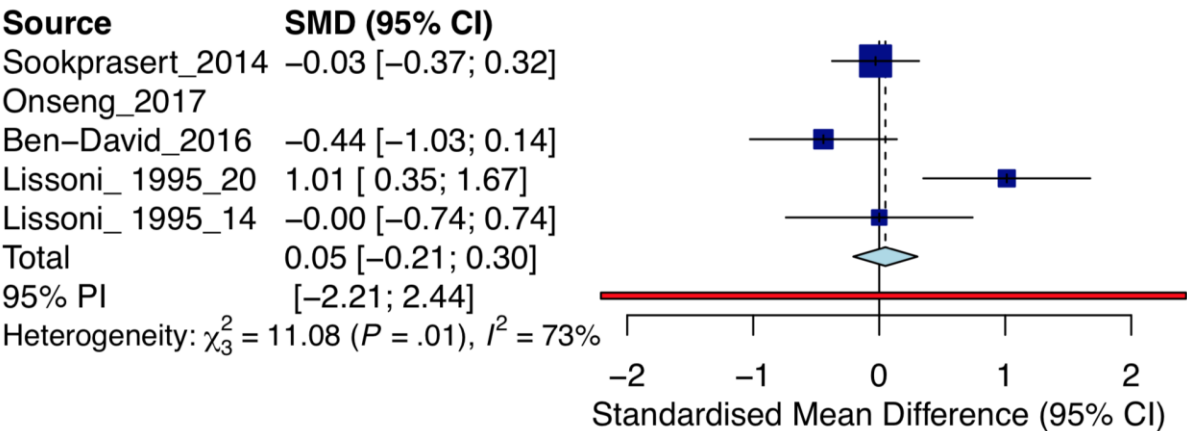


Figure 4.

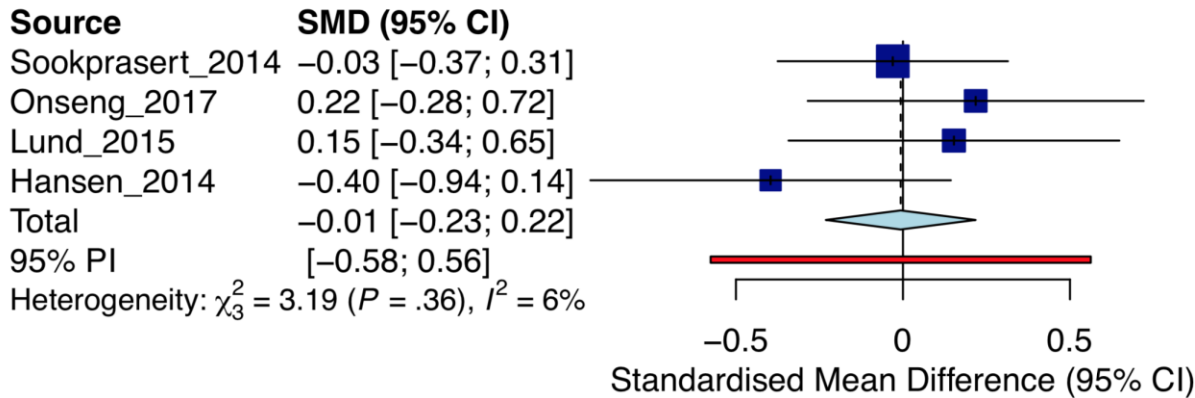


Figure 5.

Tables

Table 1. Quality Assessment of Included Studies					
Study	Randomization	Allocation Concealment	Blinding Status	Placebo/ Control	Loss to Follow-Up or Death
Sookprasert 2014	Yes	Yes	Yes	Yes	96/151
Onseng 2017	Yes	Yes	Yes	Yes	5/39
Ben-David 2016	Yes	Yes	Yes	Yes	0/47
Lund 2015	Yes	Yes	Yes	Yes	32/72
Hasen 2014	Yes	Yes	Yes	Yes	11/54
Innominato 2015	No	No	No	Yes	9/41
Del Fabbro 2013	Yes	Yes	Yes	Yes	24/48
Vigore 2010	No	No	No	Yes	0/20
Lissoni 1995	No	No	No	Yes	0/14
Lissoni 1995	No	No	No	Yes	0/20
Lissoni 1997	Yes	No	No	Yes	0/80
Lissoni 1999	Yes	No	No	Yes	0/250
Lissoni 1994	Yes	No	No	Yes	0/80
Lissoni 2008	Yes	No	No	Yes	Not Stated

Table 2. Included Non-Lissoni Study Characteristics

Author	N	Mean Age	Diagnosis and Staging	Intervention	MLT dose (mg/dl)/ Timing	Treatment Duration	HRQoL (T/C)	Survival	Treatment Related Side Effects
Sookprasert	151/56.3		Non-Small Lung Metastatic	Chemo + MLT vs. Chemo	10 or 20 qhs	7 Months	65.35/55. 85	No difference *	MLT: Fatigue (89/100), Anorexia (82/100), Neuropathy (62/99), Anemia (48/102), Thrombocytopenia (6/146) Placebo: Fatigue (39/45), Anorexia (31/45), Neuropathy (31/46), Anemia (26/46), Thrombocytopenia (2/46)
Onseng	39/48		Head and Neck	Chemo + MLT pill + MLT oral gargle vs. Chemo + placebo	10 of .2% MLT oral gargle 15 minutes before Chemo	7 Weeks	105.2/101 .0	--	Oral Mucositis (higher grade (3 and 4 vs. 2 in control; MLT onset was 16 days later than control): (T=17, C=16), Xerostomia (T=17, C=15) was not different
Ben-David.	47/54.5		Breast Stage 0-II	Chemo/radiation + MLT cream vs. Chemo/radiation + placebo	20 qhs MLT Praevoskin Cream** BID	7 Weeks	--	--	radiation-induced dermatitis (T: 9/C: 17)
Lund	72/62		GI, lung, breast, Gynecological , and other Stage IV	PC + MLT vs. PC + placebo (crossover)	20 1 hr before bed	17 days (part 1) 5 weeks (part 2)	Δ 2.9	--	No difference in appetite, fatigue, or insomnia
Bush	54/55.5		Breast Cancer Stage 1-111	Post-op surgery + MLT vs. post-op surgery + placebo	6 1 hr before bed	13 Weeks	--	--	Depressive Symptoms (T: 3/27 C:9/20)
Innominato	41/55.4		Metastatic Breast Cancer	Hormonal Therapy + MLT	5 qhs	2 Months	75/68	--	Δ -0.06 r24 (circadian rhythm marker) and 40% decrease in sleep fragmentation; no Δ in cortisol
Del Fabbro	48/60.5		Advanced lung and GI	PC + MLT vs. PC + placebo	20 qhs	28 Days	No difference	No	No difference in appetite or body weight
Vigore	20/61		Metastatic solid tumor***	MLT (no anticancer tx scheduled)	20 qhs	3 Months	--	1/20 PR, 11/20 SD, and 8/20 PD	Normalized T-reg cells (4/9) [in vitro; part 2 of study]

Abbreviations: Chemo: chemotherapy, PC: palliative care, qhs: every night before bed, hr: hour BID: twice daily, PR: partial response, SD: stable Disease, PD: progressive disease

*only MLT patients left at 22 months

** dosage unknown

*** (non-small lung, colorectal, breast, prostate, pancreatic)

Table 2. Included Lissoni Study Characteristics			
Intervention/Study Publication	MLT Dose (mg/d)	MLT Tx Duration	Survival
MLT + IL-2 immunotherapy (1995)	40 qhs	37 days	N/A
MLT + IL2 immunotherapy (1995)	40 qhs	5 weeks	N/A
Chemotherapy + MLT vs. Chemotherapy alone (1997)	20 qhs	6 chemo cycles	MLT: 1 CR* (lung), 11/39 PR**, TR (CR+PR) same
Chemotherapy + MLT vs. Chemotherapy alone (1999)	20 qhs	8 chemo cycles	1-year survival higher in MLT Chemo alone: 0/126 CR, 19/126 (PR) MLT: 6/124 CR; 36/124 PR; TR higher in MLT (42/124 vs. 19/126)
IL2 + MLT vs. IL2 (1994)	40 at 8:00 pm	5 weeks	1-year survival higher in MLT (19/41 vs. 6/39) MLT: CR=3/41, PR 8/41, TR= 11/41, SD 12/41
Supportive care vs. supportive care + MLT vs. MLT + IL2 (2008)	20 qhs	13 weeks	IL2 alone: 0/39 CR, 1/39 PR, TR: 1/39, 11/39 SD MLT: 0/285 CR, 10/285 PR, 79/286 SD, 196/286 PD MLT + IL2: 4/275 CR and 47/275 PR, TR = 51/275, 116/275 SD, 108/275 PD Supportive care: 16/285 SD, 196/286 PD
Abbreviations: qhs: every night before bed, tx: treatment, chemo: chemotherapy, PR: partial response, SD: stable disease, PD: progressive disease, TR: tumor regression			