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**Case Study: MALIGNANT MELANOMA MANAGEMENT USING THE INTEGRATED  
HEALTH CLINIC APPROACH**

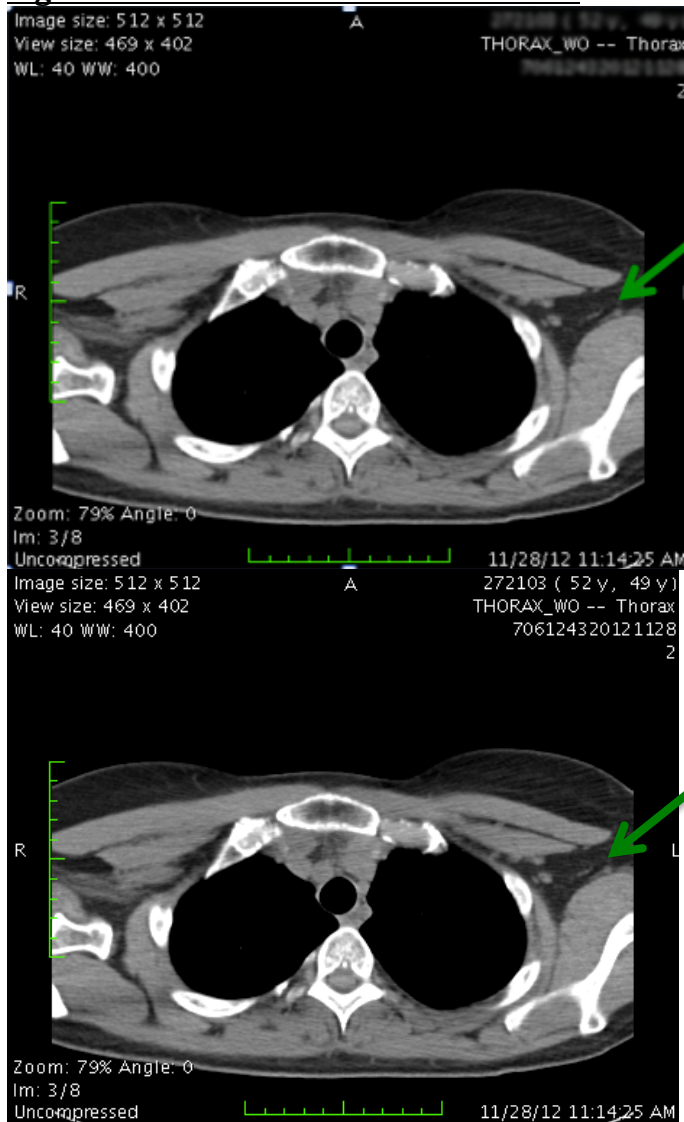
**Introduction:**

Melanoma is the most serious form of skin cancer and the sixth most common cancer in North America<sup>1</sup>. It occurs predominantly in adults, and more than 50% of the cases arise in apparently normal areas of the skin<sup>2</sup>. Risk factors include UV exposure, genetic susceptibility, history of non-melanoma skin cancers, and immunosuppression<sup>3,4,5</sup>. Treatment options depend on the presence of metastasis but may include surgical resection, immunotherapy, targeted inhibition of MAP kinase pathways, and/or radiation over affected sites<sup>6</sup>. Prognosis is dependent upon primary tumor thickness, presence of ulceration, mitotic rate, and presence/extent of metastatic disease<sup>7 8</sup>. Despite the multitude of treatment options available, the incidence of melanoma continues to drastically rise with no appreciable reduction in mortality rate. Smaller scale studies have noted tumour cell response to integrative modalities including injection therapies, targeted supplementation, hyperthermia and off-label pharmaceuticals. In this report, we present a case of malignant melanoma treated at the Integrated Health Clinic (IHC) that responded well to advanced naturopathic protocols including hyperthermia, in conjunction with disease-specific dietary, supplementary, injection and intravenous therapies.

**Case history:**

A.R. is a 49 year-old female who was diagnosed with malignant melanoma of the left lower back in May 1993. She underwent a wide local excision and pathology showed clear margins with a Breslow depth of 1.75mm. No adjuvant treatment was recommended at the time, and there was no evidence of any recurrence with her intermittent follow-ups over the following 18 years. In November 2011, she noticed a mass in her left axilla. The mass was biopsied and pathology showed positive for a melanoma metastasis. In January 2012, an excisional biopsy was done and pathology confirmed metastatic malignant melanoma demonstrating V600E BRAF mutation. She remained symptomatically well until November 2012 when a CT scan was done and again revealed the presence of nodules in the left axilla and adjoining lateral left chest wall, consistent with regional melanoma metastases (Figure 1). She was recommended further surgery and adjuvant systemic therapy, but she refused.

**Fig. 1. CT of the chest - November 2012**



AR came in for her initial consultation at IHC October 2012. A six week treatment was recommended including loco-regional hyperthermia (LRHT) 3x weekly to the left breast and axilla, fever-range whole body hyperthermia (FR-WBHT) once weekly, IVAA once to twice weekly, and oral targeted supplementation consisting of nutraceuticals and pharmaceuticals (Table 1). AR tolerated this naturopathic treatment protocol well, reporting no significant side effects. From December 2012 to May 2013, A.R. received a total of 35 LRHT and 12 FR-WBHT treatments. She tolerated both forms of hyperthermia well with no observed or reported adverse effects.

**Table 1. - Treatment Protocol**

Medication	Dosage	Effect
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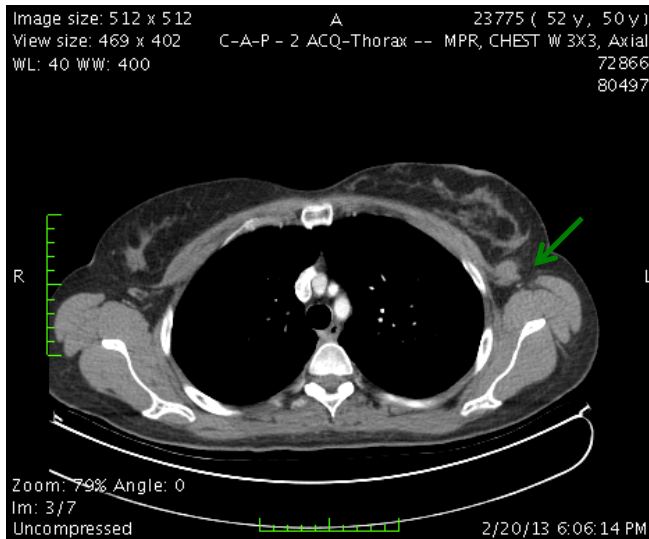
Tamoxifen	5 mg tablet p.o. OD	Induce apoptosis through inhibition of protein kinase C and inhibit angiogenesis <sup>9,10</sup> The active metabolite endoxifen demonstrate cytostatic activity over melanoma cells <sup>11</sup> .
Celebrex	100mg capsule p.o. BID	Inhibit cyclooxygenase-2 (COX2) enzymes. Blocking COX 2 decrease tumor invasiveness <sup>12</sup> Induce apoptosis and inhibit angiogenesis of tumor cells <sup>13</sup>
Cimetidine	400mg tablet p.o. BID	Repurposed as an anti-cancer agent <sup>14</sup> Anti-adhesion (cadherins) and antiangiogenesis, Inhibit tumor cell propagation and metastasis <sup>15</sup> . Enhance host immune response and block cell growth promoting activity of histamine in melanoma cell lines <sup>16</sup>
Metformin	250mg tablet p.o. BID	Activation of AMPK may result from a mild inhibitory effect of metformin on mitochondrial complex 1, which in turn would raise AMP and activate AMPK <sup>17</sup> Decrease insulin (promotes cancer cell growth) resistance and reduces insulin level. Direct inhibitory effect on cancer cell growth and antitumoral action <sup>18</sup>
Low Dose Naltrexone	2.5mg tablet p.o. h.s.	
Thyroid capsules	30mg capsule p.o. o.d.	Suppresses TSH, which is shown to induce proliferation of melanoma

		cells <sup>19</sup>
<b>Supplements</b>		
Iscador	SQ 3x/week	Prolong survival time and stimulate self-regulation <sup>20</sup> Early cycle inhibition followed by apoptosis in a dose dependent manner <sup>21</sup>
IV Alpha Lipoic Acid*	1-2x/week	Induce apoptosis in cancer cells. Stabilize NF-κB transcription factor <sup>22</sup> Inhibit glycolysis <sup>23</sup>
IV Ascorbic Acid (25G)*	1-2x/week	Improve quality of life, decrease tumor size and prolong relapse interval <sup>24</sup> Alleviates cancer and chemotherapy related symptoms <sup>25</sup>
Melatonin	20mg tablet p.o. h.s.	Immunomodulatory. Augment production of T-lymphocytes and NK cells. Oncostatic properties in melanomas and tumors of epithelial origin <sup>26</sup> Benefits seen on survival rates, treatment response rates, disease progression, and toxicity profile <sup>27</sup>
EGCG	1 capsule p.o. BID	Anti-proliferative and pro-apoptotic to melanoma cells <sup>28</sup> Inhibit growth and invasive potential of melanoma cells <sup>29,30,31</sup> Immunomodulatory and pro-inflammatory mediator production <sup>32</sup>
CoQ10	100mg capsule 2-3x/day	Decrease recurrence rates of melanoma <sup>33</sup>
Vitamin D3	5,000-10,000 I.U./day	Increased circulating levels of vitamin D are associated with reduced occurrence and a reduced mortality in different histological types of cancer, including those

		<p>resident in the skin, prostate, breast, colon, ovary, kidney, and bladder<sup>34</sup></p> <p>Maintenance of normal differentiation, enhancement of apoptosis, and prevention of tumor angiogenesis<sup>35</sup></p>
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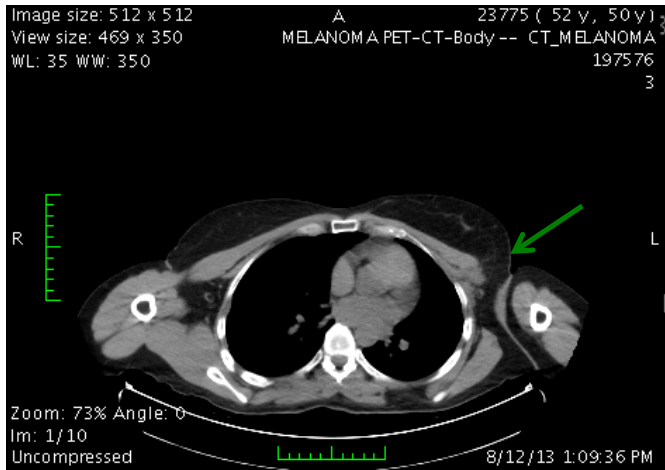
In February 2013, CT scan of the chest and PET /CT showed improvement of the metastatic melanoma within the left chest wall (Fig 2). She continued with naturopathic treatments and remained stable with a good quality of life.

**Figure 2. CT of the chest – February 2013**



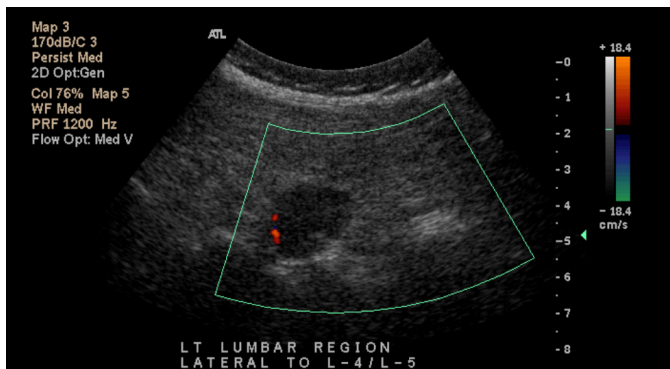
In August 2013, a restaging PET/CT scan was done and revealed smaller hypermetabolic nodules in the left axilla and two adjoining hypermetabolic nodules in the left chest wall adjacent to the intercostal space. (Fig. 3). At this point, AR started on GcMAF injections once a week for 6 months, under the recommendation of another healthcare provider.

**Figure 3. Restaging PET/CT – August 2013**



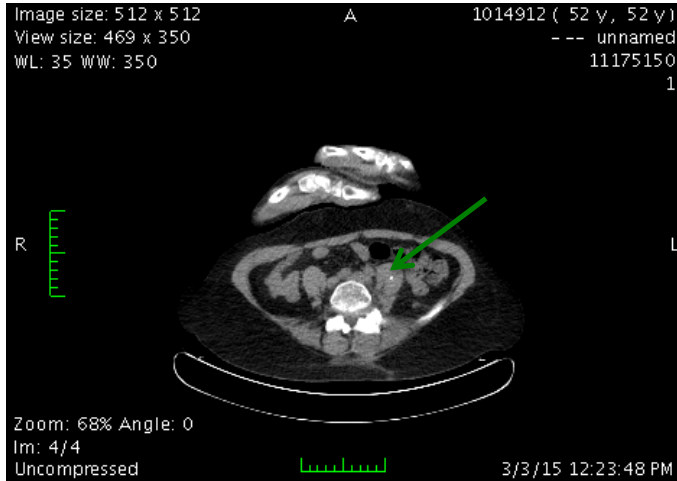
In October 2013, AR was recommended operative intervention with exploration of the axilla. She underwent left axillary nodal dissection and the final pathology revealed recurrent metastatic melanoma affecting seven out of twelve lymph nodes. She refused chemotherapy despite the aggressive histologic appearance of the tumor. Instead, AR opted to repeat her hyperthermia protocol to the left axilla from November to December 2013 completing 16 treatments. Again, she remained asymptomatic having a good quality of life until March 2014 when she started experiencing back pain. An MRI showed metabolic activity near L4 and L5, and an ultrasound biopsy confirmed the presence of recurrent melanoma. (Fig. 4)

**Figure 4. Ultrasound guided biopsy - L4 mass- April 2014**

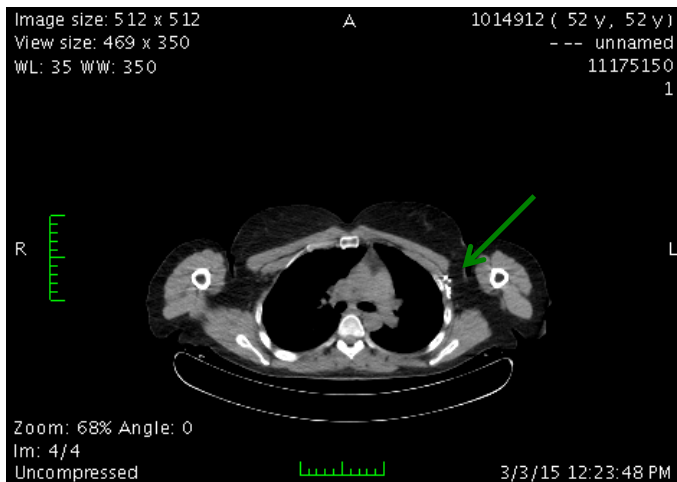


AR refused recommendation for systemic chemotherapy but elected to proceed with operative intervention for the spinal mass and to continue with naturopathic treatment protocol. The spinal mass was subtotally resected due to proximity to neural structure; hence, stereotactic body radiation therapy (SBRT) was done postoperatively to the operative bed in September 2014. A follow-up PET CT was done in March 2015 and results showed a mild uptake in the treatment area along L4-5 with an SUV 2.9. (Fig 5.) The avid lymph node in the chest wall is slightly larger but stable with an SUV of 2.3. (Fig 6.) There are no new uptakes seen.

**Figure 5 – PET/CT Lumbar area – March 2015**

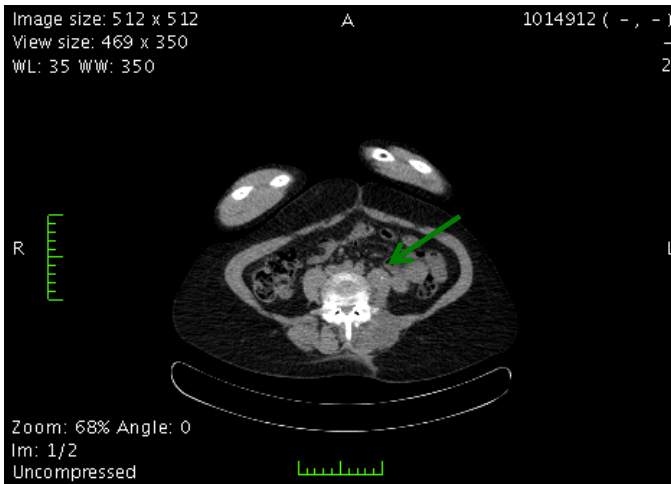


**Figure 6 – PET/CT Chest – March 2015**

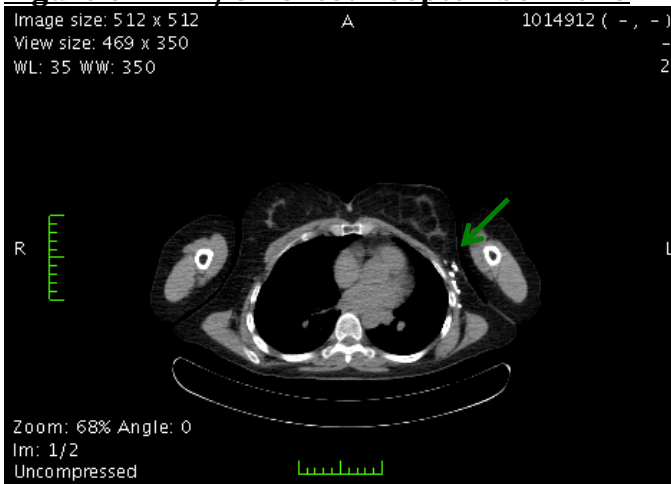


In September 2015, a PET/CT was done and results show stable, mildly hypermetabolic inflammatory changes in the left lumbar paraspinal musculature (Fig. 7). There is a stable, mildly hypermetabolic subpectoral lymph node in the left with stable postoperative inflammatory changes in the chest wall and axilla. There is no evidence of locoregional recurrence of melanoma (Fig. 8).

**Figure 7 – PET/CT Lumbar area – September 2015**



**Figure 8 – PET/CT Chest – September 2015**



### **Discussion:**

The incidence of melanoma continues to rise and despite efforts to heighten early screening techniques, there has been no reduction in mortality<sup>1</sup>. There is a steady rise in incidence of malignant melanoma, and in the United States epidemiological studies from 1982 to 2011, reported a two-fold increase in melanoma cases<sup>36</sup>. It is therefore essential to investigate other adjunctive therapies to manage this aggressive disease. This case report demonstrates the potential effectiveness of an integrative plan for malignant melanoma combined with surgery.

When used as a singular modality, hyperthermia has shown improvements in both partial and complete response rates for several malignancies including squamous cell cancers, adenocarcinomas, and melanomas<sup>37</sup>. In an overview of methods for drug delivery to tumors, research shows that reduction of TIFP (Tumor Interstitial Flow Pressure) was temperature and time dependent. The reduction of TIFP was associated with an increase in perfusion and a sustained reduction of hypoxia,

which led to an improvement in antitumoral effects when associated with chemotherapy and radiotherapy<sup>38</sup>. Elevated temperatures influence lymphocyte transformation and mitogenesis, both of which increase the activity of the immune system. The systemic activation of the immune system by hyperthermia may help target metastatic tumour cells<sup>39</sup>. Hyperthermia relies on the unique characteristics of malignant cells, and acts on these mechanisms to inhibit its growth. Compared to healthy tissue, malignant cells are more sensitive to high temperatures. Tumor cell architecture and vasculature is more chaotic compared to healthy tissue, and this leads to an immature, structurally defective microvascular system that is less resilient to perfusion shifts. The morphology, membrane fluidity and gene expression of a cancer cell also differs from normal cells. Heat increases membrane fluidity and instability of cancer cells, leading to cell death directly or indirectly through increased delivery of cytostatic chemotherapy agents. Heat induces expression of p53, a tumor suppressor transcription factor that is mutated or decreased in cancer cells. Hyperthermia also induces protective anti-tumor immune responses by presenting the tumour peptides to naïve T-cells in the draining lymph nodes. The lymphocytes will mature and proliferate into cytotoxic T lymphocytes and CD4+ helper cells, mounting an adaptive immune response against tumour cells<sup>37</sup>.

### **Conclusion:**

This case report demonstrates that integrative oncology treatment is safe and effective for the management of metastatic melanoma. Melanoma being an aggressive disease should be managed using all possible resources. The use of naturopathic treatments played an important role for the patient's wellness and quality of life. Hyperthermia in combination with targeted supplementation has shown to be effective in the management of malignant melanoma with fewer side effects.

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