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EDITORIAL

Mathematical Modeling of Acupuncture as Cancer Symptom Therapy: First Steps

The practice of acupuncture (AP) is frequently traced to the Emperor Huangdi, whose *Classic* includes descriptions of the practice hundreds of years before the Christian era [1]. The practice has come far towards integration in modern medical practice in the intervening millennia, especially in the management of symptoms referable to cancer or its treatment [2]. However, the modern practice of acupuncture mirrors the modern practice of radiation therapy (RT) in that treatment schedules are practical rather than evidence-based.

Clinical delivery of radiation therapy has a far briefer history than acupuncture [3]. Its use was first reported in 1899, in patients with skin cancers [3]. Since then, the practice has emerged as a critical tool in the treatment of cancer, and the disciplines of radiation oncology, radiation biology, therapeutic physics, and medical dosimetry have grown in stature and sophistication. However, conventional radiation delivery involves daily treatments, often delivered for weeks, and not including weekends or holidays in almost all cases.

The case has been made that—given the fact that tumors and normal tissues continue basic processes over the weekends—perhaps RT should be routinely delivered then also. This argument ignores the obvious fact that a daily delivery during the work week may be similarly naïve. In fact, the current practice of RT is based on decades of experience in most cases that: (1) outcomes; and (2) toxicity may be predictable (not necessarily optimal) with five daily treatments weekly. Regimens with 7-weekly fractions or 2—3-daily fractions have been published, but patients so treated are in the vanishing minority.

We have been interested in optimizing RT delivery based on established data that take into account tumor repopulation [4] and death [5] characteristics, and repair of sublethal RT damage [6]. Initial forays into such models provided the predictable result that, given a 5-day regimen, more doses should be given on the fraction immediately prior to any treatment break [7]. Whether because of practical considerations, ignorance of the data, or disbelief, this is never done in the clinic. A new push for translating mathematical models of RT fractionation may be provided by more recent quantitative comparisons of different clinically applied protocols [8,9] and novel protocol optimization [10], which have, at least in part, been tested and validated *in vivo*.

In this vein, similar attention could be paid to acupuncture. For instance, in the case of acupuncture for xerostomia, regimens differ drastically in different reports [11—14]. These different regimens may be modeled as RT delivery has been modeled. Coarse inroads have been made into quantifying different acupuncture techniques and treatment responses using mathematical modeling [15,16]. However, the modeling process for acupuncture is far more complex than for RT. Although RT is delivered uniformly in five daily treatments per week, modern acupuncturists use regimens varying in duration (total time of treatment), intensity (number of fractions per week), and dosage (length of each session), regardless of whether stimulation (electric or moxibustion) is used. Taking all these factors into a single model is unwieldy beyond practicality.

Another option is to model results and then work backwards to the protocols—whether RT or AP—that produced them. Under these circumstances, the best tool for modeling would be objective results obtained by a particular regimen. The problem with most of the current AP data in the symptom control arena is that objective results are very infrequently obtained; the usual result data are patient-reported, subjective outcomes. Of the studies listed above, three used objective measurement of salivary flow rates [11,13,14], although only two obtained both basal and stimulated flow [11,13]. Thus hindered by lack of published data, generating acupuncture isoeffect models is challenging.

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Given such data, though, interesting results may be obtained. For instance, consider a recent clinical trial of acupuncture for sleep disturbance and hot flashes in breast cancer patients [9]. Community acupuncture providers provided three treatments over a 2-week period after demographic and treatment data were collected during a baseline assessment. Physiological monitoring using wrist actigraphy and hot flash monitoring occurred during the 2-week baseline period, then during the 2 weeks of acupuncture and twice in follow-up during Week 5 and Week 8 of the trial.

Data regarding sleep latency (amount of time required to go to sleep once abed) are available [17]. During the 2-week baseline, sleep latency for the cohort was 17.89 minutes (SD. 6.12). During the 1st week of acupuncture the latency decreased to 15.26 minutes (SD 14.19), and fell further to 14.73 minutes (SD 14.80) during the 2nd week. During the first follow-up week (Week 5 of the trial), the value had a nadir of 10.21 (SD 8.09), and by the 8th week had returned to 24.08 minutes (SD 17.37). These data are consistent with a progressive response to increasing acupuncture dose, with maximal effect 1 week after completion before extinction. As data beyond Week 8 are unavailable, it is unclear whether the 24.08 minute latency at 8 weeks is a return to baseline or an exaggerated "rebound" response.

Data regarding daily hot flashes as determined by sternal skin conductance also show a treatment effect followed by extinction. Baseline values were 12.58 hot flashes daily (SD 13.41), followed by 11.37 daily (SD 11.19) during Week 3 and 13.22 daily (SD 14.32) during Week 4. As opposed to the sleep data, the effect required three treatments: nadir was reached during Week 5 [8.95 daily (SD 11.65)]. Similar to the sleep data, extinction of effect by 3 weeks later [13.06 daily (SD 11.53)] was evident.

Before engaging in formal model construction more data are required, but such is the nascent state of acupuncture data currently. Well-constructed AP trials yielding objective data are scarce, and if published are not replicated. Such data are necessary for substantive isoeffect models, as exist currently for RT. Given such models, then we might address the thornier issue of modeling the AP practice itself.

Disclosure statement

The authors declare that they have no conflicts of interest and no financial interests related to the material of this manuscript.

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