A New Title, A New Platform—Welcome to CANDJ

Marianne Trevorrow,[1] MA, ND

This letter begins a new chapter for the Canadian Association of Naturopathic Doctors (CAND) and this publication; after almost a year of behind-the-scenes work by the editors, CAND Executive staff and Chair, and SG Publishing, we are launching the new *CAND Journal* on a digital platform, with issues archived from the beginning of 2019 through to our current one.

The planning for this move has been in motion for several years. There is much more to an indexed naturopathic medical publication than simply placing articles online, and much of that has to do with editorial production standards that are crucial to creating high-quality, scholarly, independent content. Peer review, for example, is a critical factor in assuring scientific accuracy, and we have been building an international pool of reviewers with institutional, academic, and research affiliations who are able to give timely, appropriate, and helpful feedback to our authors. At the same time, clear and robust conflict-of-interest guidelines create transparency about potential bias when content or authors are sponsored by industry. This isn't to say that we don't welcome sponsorship, and certainly our publication could not function without the support of our advertisers and corporate partners, but key to our credibility with the public (as well as our members) is that we make these relationships clear so that readers can draw their own conclusions about whether these interests affect what the authors have written.

Additionally, our new comprehensive submission and review guidelines will make our standards clear to everyone. All the articles we publish will be carefully vetted for accuracy, originality, and relevance to our professional naturopathic audience. Both submission and peer review will be managed online though the Open Journal Systems (OJS) platform, streamlining the process for authors and reviewers, and creating a more transparent peer review process for everyone. Finally, we will have post-review editing through SG Publishing to ensure that articles adhere to professional style standards, including referencing.

At every step, we also reflected on what makes us *unique* as a naturopathic medical publication, especially our central role as a voice for Traditional & Complementary Medicine (T&CM), Indigenous and planetary health, and patient-centred care that embraces health equity. We made sure that with all our movement towards transforming *Vital Link* to *CANDJ,* we didn't lose sight of the naturopathic principles and philosophy that brought us here. We are also clear in our new Aims & Scope statement for the journal that, at *CANDJ,* there will always be a place to discuss the humanistic aspects of healing, areas that may never be amenable to "gold standard" randomized controlled trials (RCTs) or the narrowly focused evidence-based models of care.

To lead off this edition, a letter from our CAND Chair, Mark Fontes, and a commentary from Ellen Conte at the Canadian College of Naturopathic Medicine (CCNM)'s Patterson Institute for Oncology Research and the Halifax Naturopathic Health Centre, discuss the importance of the work that has gone into this transition and the anticipated benefits of online indexing for knowledge translation and advancement of ND-led research, both in Canada and internationally. Next, Iva Lloyd, the current president of the World Naturopathic Federation, reports on work the Federation has done to survey how research is translated into naturopathic practice and some of the barriers that ND-led research has had in reaching wide uptake by practising clinicians. One fascinating detail this work has shown is that while there are few indexed naturopathic journals operating internationally (we will be one of the first), naturopathic research articles published in other indexed platforms mention the term "naturopathy" less than 8% of the time. This is a sobering statistic, and is one of our primary motivations in connecting our researchers and clinicians so that we can have more productive conversations about evidence-based practices (EBPs) that are appropriate to ND clinical decision-making.

Along those lines, Aucoin, Leach, and Cooley from CCNM in Toronto and Southern Cross University in Australia report on their recent cross-sectional study of EBP knowledge and use by Canadian NDs, part of a larger international EPICENTRE project on EBP uptake by Complementary and Alternative Medicine (CAM) practitioners. Their study found that over 70% of participants based clinical decision-making on evidence from clinical research. They also found a predominantly favourable attitude towards EBP among participants, although there was also a self-recognition that many clinicians have had little exposure to how CAM research is conducted.

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Our final article for this edition is a literature review by Conte, Psihogios, and Seely on hyperthermia in cancer care. Until now, this therapy has not been well known outside of facilities dedicated to naturopathic cancer care, which is itself a very small proportion of ND practices in North America. This comprehensive review should fill a crucial knowledge gap in this area by surveying the evidence published to date on safety, efficacy, and best use.

Finally, and on a personal note, I would like to congratulate our Associate Editor, Cyndi Gilbert, on being designated Naturopathic Medical Student Association (NMSA) Faculty of the Year at their annual conference, right before the publication deadline. Since she came on board at *CANDJ* last summer, Cyndi has helped us expand our writing mentorship program to ND students and early career clinicians. This has served to enrich and expand the kinds of articles we publish and to advance the conversation in the profession on many novel areas of practice, including health equity.

We hope our members find our new web platform easy to navigate and enjoy enhanced access to our recent back issues, including our new Editor Selections, which provides quick access to articles chosen based on their significant and potential impact on the field of naturopathic and integrative medicine.

As always, we encourage both our members and wider audience to submit to future editions and help strengthen the conversation about naturopathic best practices within the wider Canadian regulated healthcare community.

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History and Evolution of the *Vital Link* Journal

Mark Fontes, ND, and **Shawn O'Reilly**

The history and evolution of the *Vital Link* mirrors, to a large degree, the growth of naturopathic medicine in Canada. The *Vital Link* has been published by the Canadian Association of Naturopathic Doctors (CAND) (then the Canadian Naturopathic Association, CNA) since 1992, when practising naturopathic doctors (NDs) in the country numbered around 500. Between 1992 and 2008, as the profession grew to over 1,000 NDs, the *Vital Link* was published as a newsletter for CAND members and included professional updates, CAND-related news, and general articles written by NDs. In 2008, the decision was made to establish the *Vital Link* as a peer-review-style journal featuring scholarly articles about naturopathic medicine. Its layout was updated to reflect this new direction. The following year, an editorial/review board was established. In 2011, with over 1,500 NDs in practice, the journal underwent a substantial revision focusing on the cause of disease, with each edition providing an in-depth review of one topic. The layout, masthead, and graphics were completely redesigned. Since that time, the *Vital Link* has only contained research-based articles that have undergone peer review alongside a CAND Update. It is important to note that with the exception of an outside printer, all the work required to publish the *Vital Link* was done in house and by a dedicated group of NDs volunteering their time as editors, authors, and reviewers.

Since its inception, the *Vital Link* journal's objectives have been to increase professional and public exposure to its articles, create a more prominent profile for naturopathic doctors and, in the long term, to become indexed in Alternative Medicine and Conventional Medicine databases. With NDs in Canada now numbering over 3,000 and with the launch of the *CANDJ*, we are proud to say that we can now put a tick mark beside that final objective.

The *CANDJ* serves as an important resource for the naturopathic profession to provide research updates on best patient care practices and evidence-informed treatments. We look forward to growing the research base of the naturopathic profession and engaging in conversations with our colleagues and allied health professionals.

We would like to thank everyone who has been involved in making this important transition a reality: Dr. Marianne Trevorrow, ND (Editor in Chief), Dr. Cyndi Gilbert, ND (Associate Editor), and Jill Torigian and her team at SG Publishing. On behalf of the naturopathic profession, thank you for your time and commitment to producing a high-quality and valuable online journal.

Dr. Mark Fontes, ND, is Chair of the Canadian Association of Naturopathic Doctors.
Shawn O'Reilly is Executive Director and Director of Government Relations of the Canadian Association of Naturopathic Doctors.

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The Value of Going Digital for Canadian Naturopathic Doctors and Researchers

Ellen Conte[1,2]

The *Canadian Association of Naturopathic Doctors Journal (CANDJ)*, formerly *Vital Link*, has been the journal of the Canadian Association of Naturopathic Doctors (CAND) for over 25 years, but this edition is different. This is the first digital version of the Association's publication. This may seem a small or even inevitable change to many, but it is an important step in the direction and future of the *CANDJ* and naturopathic doctor (ND)-led research in Canada. The move to a digital format allows for greater access and readership, opens up the opportunity for scholarly database indexing, reduces barriers to publication for ND researchers, and supports the inclusion of evidence and research in naturopathic practice.

The digital platform for the *CANDJ* immediately allows for greater reach and readership, which will enhance knowledge translation, the process by which research findings are shared and implemented, which is ultimately the goal of all research. Although publication is an important aspect of knowledge translation, it is only effective if it is accessible. The online format will allow for more people, especially those outside of the CAND, to find and read the journal.

The most important extension of this enhanced discoverability is the potential for scholarly database indexing, making papers accessible through common databases such as PubMed, Cochrane Library, and Google Scholar.[1] For research to reach the healthcare providers and researchers who could use the information (often referred to as the end user), the paper needs to be discoverable. Most of us turn to well-known databases such as those mentioned, but only journals indexed by these databases will be found through their search engine. Thus, indexing is essential for research to have an optimal impact, and the move to a digital platform is the first step in this process. Indexing is also considered a reflection of the quality of the journal; databases typically only accept journals of sufficient quality. Thus, the very act of becoming indexed enhances the perception of journal quality. Lastly, indexing is important for the individual authors. The greater reach their work gets, the greater their individual impact can become. Thus, indexing will help to attract high-quality submissions as authors will receive the recognition they deserve for their work.

The *CANDJ* provides a location for ND clinicians and researchers to publish their work in a peer-reviewed journal without an article processing fee. This eliminates a common barrier to research and publication, which could encourage more NDs to share their findings. The more NDs participate in research and sharing findings, the stronger the profession will be.

All of these aspects—greater readership, scholarly database indexing, and an avenue for ND-led research publication—ultimately support and enhance the inclusion of research into naturopathic practice and health care in general. Isn't that the ultimate goal of research, to change and improve the way we care for our patients? The more we study, write, publish, and share, the stronger the foundation of our medicine becomes.

Research on complementary and alternative medicine (CAM) therapies has boomed in the past couple of decades,[2] and journals like the *CANDJ* provide the opportunity for NDs to publish research findings and contribute to the growth of CAM evidence. The move to digital represents an exciting advancement for the journal, with great opportunities for the future. Congratulations and thank you to Editor Marianne Trevorrow, and many others who worked to make this transition happen. Naturopathic research continues to expand and shape how we practise, and this is another step in that trajectory.

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The Breadth and Depth of Naturopathic Research

Iva Lloyd,[1] ND

Over the last five years, the World Naturopathic Federation (WNF) has undertaken the task of determining the breadth and depth of research available to support naturopathic practice. This initiative has had some significant results, including the recognition that believing naturopathic practice is not supported by research is outdated. The following highlights the information that the WNF has gathered on naturopathic research.

TYPES OF RESEARCH

Four main types of research are used to support a healthcare practice:

- **Traditional research** includes the research passed down by naturopathic elders, information in naturopathic texts, and the knowledge gathered through practice.
- **Borrowed research** is the research that others have done on aspects of naturopathic practice.
- **Research done by the profession** encompasses the case studies, reviews, original clinical research, surveys, and other research studies conducted by the naturopathic community.
- **Research done on the profession** is a sign of professional development and recognition, when naturopathic practice is included in the research done on traditional, complementary and integrative medicine (TCIM) by other researchers and/or when naturopathy/naturopathic medicine is included in prevalence-of-use studies and other surveys and research done by governments.

Traditional Research

There has been ongoing debate in the naturopathic profession over the last decade concerning a move away from traditional knowledge as the basis for naturopathic practice. In 2020, the WNF supported an international survey examining naturopaths'/naturopathic doctors' approach to sharing and using knowledge and information related to their clinical practice. The survey was translated into five languages and resulted in 548 responses from naturopaths/naturopathic doctors around the world. The results indicated a very balanced mix of using scientific knowledge and traditional knowledge.[1] For example, participants most commonly reported using information published in scientific journals (76.2%) to inform the care they provided to their patients, and most of the participants who used this information source reported doing so "most of the time." Information provided by the patient was selected by participants as a source that they used (64.6%), yet the majority (81.7%) of the participants who use that information indicated they "always" do so. The knowledge types reported by participants as used to inform patient care included knowledge developed through clinical experience (86.2%, n = 412), initial clinical training (81.2%, n = 388), continuing professional education delivered by an expert clinician (79.9%, n = 382), consideration of the patient's unique needs (78.7%, n = 376), and discussions with professional peers (75.7%, n = 362). The survey highlighted that not only do naturopaths/naturopathic doctors use traditional knowledge they also provide patient-centred care as part of their practice.[1] The charts below provide an estimate of how the research supporting naturopathic practice has changed over the last 20 years (see Figures 1 and 2).

The change in traditional knowledge is more about the tremendous expansion in borrowed research and research conducted by the naturopathic profession than it is about a move away from traditional knowledge. The total body of research is greatly expanding, and research designs are now incorporating holistic, vitalistic and complex naturopathic care, and assessing more accurately the uniqueness of naturopathic practice.

Borrowed Research

Every aspect of naturopathic practice and education is influenced by the research done by other professions and other systems of medicine. Naturopathic medicine borrows research to support the mind–body connection and the important link between a patient's psychological state and their health. Borrowed research includes supporting the role of a healthy lifestyle, applied and clinical nutrition, herbal medicine, naturopathic manipulation, acupuncture and other forms of naturopathic physical medicine, intravenous therapy and injection therapies (meso- and prolo-therapy), as well as all aspects of environmental medicine and areas such as non-communicable diseases and their link to

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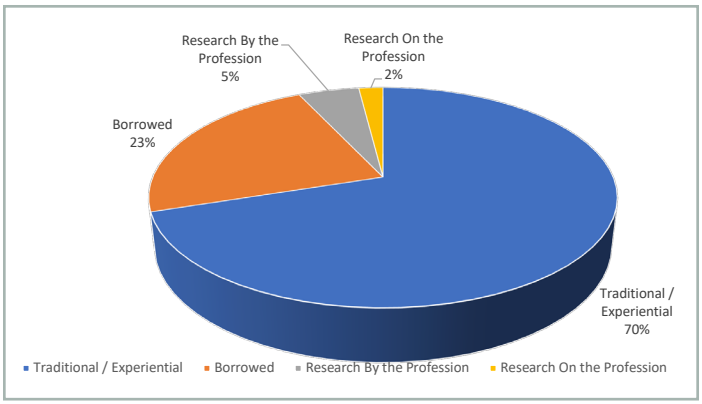

FIGURE 1 Research support for the naturopathic profession in 1999 (estimate)[2]

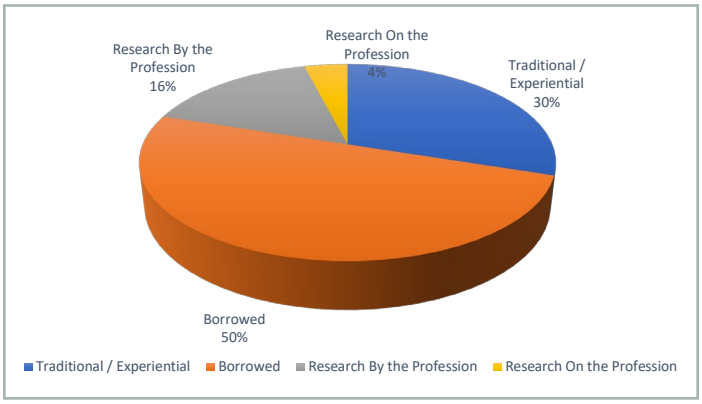

FIGURE 2 Research support for naturopathic profession 2020 (estimate)[2]

lifestyle factors or research on complex systems theory. Borrowed research is an important aspect of interprofessional collaboration and providing the highest level of care to patients based on the body of available research.

Research Done By the Profession

To determine the research done by the naturopathic profession, a bibliometric analysis was conducted from 2016 to 2018, identifying a total of 2,218 research articles. The criteria for the bibliometric analysis included research that was published in an indexed peer-reviewed journal and conducted by naturopaths/naturopathic doctors.[3] Highlights of the bibliometric analysis are as follows:

- 166 naturopathic researchers were included in the analysis; 31% of the researchers were from the United States and 19% from Canada.
- The majority of the research (53%) was conducted in North America.
- 32% of the research was affiliated with naturopathic educational institutions.
- Research designs included: 23% reviews and meta-analysis, 19% interventional trial, 18% observational studies, 16% commentaries, 10% observational trials (see Figure 3).

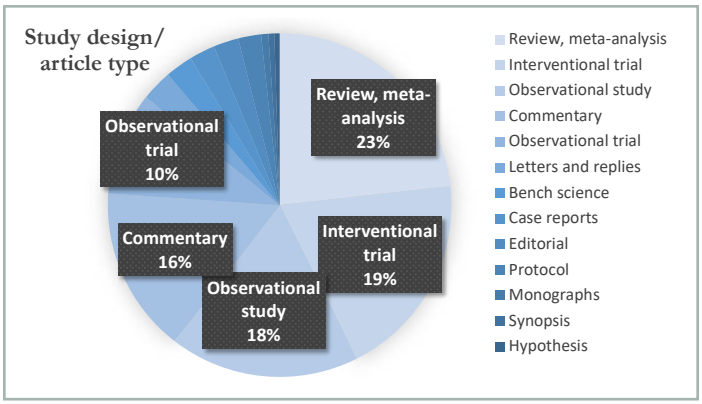

FIGURE 3 Number of naturopathic research articles published per year since 1987

- A broad range of conditions and naturopathic therapeutic modalities or practices were researched (see Table 1).
- Naturopathic researchers are publishing articles in high-ranked journals with over half of all articles appearing in 40 different journals.

The results of this bibliometric analysis were published in early 2021 in the *Journal of Alternative and Complementary Medicine* and identified that the international naturopathic research community has produced peer-reviewed literature for over 30 years and has demonstrated a sustained commitment to codifying existing knowledge, generating new knowledge, and disseminating this knowledge to the wider clinical and research community. It also identified that the naturopathic community is conducting the types of research required for development of an evidence base for naturopathic practice. Figure 4 displays the number of naturopathic articles published per year, revealing a steady increase over the last 20 years, especially in the last decade. Figure 3 shows the breakdown of study designs, indicating that naturopathic researchers are engaged in a range of different types of research.

Table 1 outlines the breakdown of the health conditions covered in naturopathic research and the range of naturopathic therapeutic modalities and practices that were researched. The research

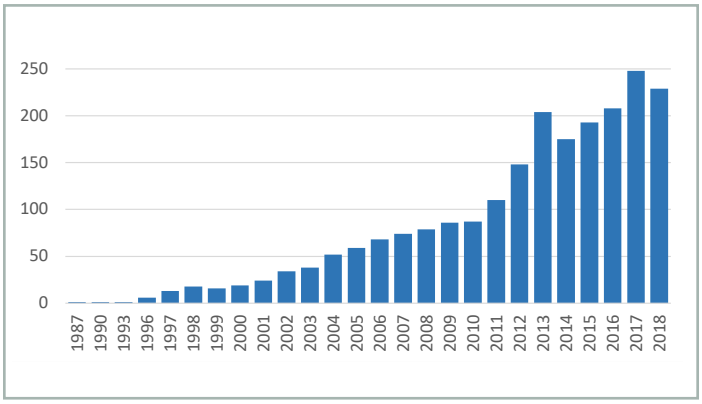

FIGURE 4 Study design and article type

TABLE 1 Characteristics of published articles in naturopathy (*n*=2,218)

Characteristics	N	%
Health condition researched		
Cancer and cancer-related condition	316	14.3
Mental health care and mental illness	273	12.3
Musculoskeletal condition	190	8.6
Neurological condition	151	6.8
Gastrointestinal condition	125	5.6
Female reproductive and sexual health	125	5.6
Cardiovascular condition	100	4.5
Endocrine condition	77	3.5
Infectious disease	71	3.2
Respiratory condition	59	2.7
Weight management	46	2.1
Dermatology condition	37	1.7
General wellness and preventive	32	1.4
Urogenital condition	24	1.1
Ageing and cognition-related disorders	20	0.9
Autoimmune condition	8	0.4
Therapeutic modality and practices researched		
Herbal/botanical medicine	403	18.2
Clinical nutrition, including supplements/nutraceuticals	317	14.3
Explicitly focusing on naturopathy	179	8.1
Yoga	192	8.7
Counseling, meditation, and mind–body medicine	165	7.4
Applied nutrition, including dietary prescription	106	4.8
Manual therapies	91	4.1
Lifestyle and behaviour changes	86	3.9
Acupuncture	53	2.4
Traditional Chinese medicine practices other than acupuncture	42	1.9
Laboratory, pathology or radiology testing	36	1.6
Hydrotherapy	16	0.7
Hormone prescribing	14	0.6
Homeopathy	11	0.5
Ayurvedic medicine other than yoga	11	0.5
Intravenous therapies	5	0.2
Wound care	2	0.1
Chelation therapy	1	0.05
Other naturopathic treatments	26	1.2

conducted by naturopathic researchers is broad, which is reflective of naturopathic practice.

One surprising outcome of the bibliometric analysis was that only 7.6% of the naturopathic research articles explicitly focused on or mentioned "naturopathy." This partially explains why some people feel that there is not a lot of research to support naturopathic practice.

Along with the naturopathic bibliometric analysis, the WNF surveyed the global naturopathic profession to understand the naturopathic journals and the type of peer-reviewed articles that they recognize. Members of the WNF identified 22 journals that are primarily focused on naturopathic content.[4] The survey also revealed that these journals house over 10,000 naturopathic peer-reviewed articles written primarily for naturopaths/naturopathic doctors and other healthcare providers. The breadth of focus on various conditions and therapeutic modalities was similar to the results of the bibliometric analysis. Unfortunately, the majority of research papers were not part of the naturopathic bibliometric analysis as they were not available in indexed journals, which was an inclusion criterion.[5] This applies to the research papers from *Vital Link*. As the previous editor of *Vital Link*, I am excited to see the changes that are occurring and the commitment of the Canadian Association of Naturopathic Doctors to ensuring that naturopathic research papers are available to a wider audience.

Research Done On the Profession

In 2021, two other bibliometric reports—one on Traditional and Complementary Medicine (T&CM) and one on osteopathy—were also published, and both showed similar trends in increased research over the last two decades.[6,7] The bibliometric analysis on T&CM identified 172,466 publications (42,331 open access), published by 219,680 authors in 143 journals from 1938 to 2021.[6] The osteopathic bibliometric analysis identified 389 research articles between 1966 and 2018.

HEALTH TECHNOLOGY ASSESSMENT ON NATUROPATHY (HTA)

The results of the bibliometric analysis, along with 10 surveys of the global naturopathic profession, provided the backbone for the WNF, with the assistance of over 50 naturopathic researchers around the globe, to compile a *Health Technology Assessment on Naturopathy* (*HTA*).[8] The *HTA* is a 600-page textbook that will be published in the fall of 2021 and will provide governments, educational institutions, naturopathic organizations, individual naturopaths/naturopathic doctors and other healthcare providers a detailed understanding of the breadth and depth of naturopathic practice around the world. The *HTA* covers the following[8]:

- Naturopathic concepts, including the philosophies, principles, and theories that define the naturopathic profession, as well as an overview of naturopathic practice and the therapeutic modalities and practices that are included.
- The status of naturopathic professional formation, including the history of naturopathy by world region and the status of naturopathic regulation and education around the world.
- An overview of naturopathic research, including challenges and opportunities, the importance of choosing research designs that match the complexity of naturopathic practice, and an overview of the naturopathic bibliometric analysis.

The section outlining the research on the effectiveness of naturopathic practice includes a breakdown of 235 original clinical research articles conducted by naturopathic researchers

highlighting 12 conditions, such as cardiovascular, complex immune, endocrine and women's health. In total, naturopathic researchers have published over 1,456 journal articles in indexed peer-reviewed journals related to health conditions and roughly half of these are reviews and meta-analyses (n = 357; 24.5%) or observational studies (n = 363; 24.9%).

The section outlining the research on naturopathic therapeutic modalities and practices includes a breakdown of 305 original clinical research articles conducted by naturopathic researchers covering applied nutrition, clinical nutritional, herbal medicine, mind–body medicine, acupuncture, yoga, and other naturopathic modalities and therapies. In total, naturopathic researchers have published over 1,203 journal articles in indexed peer-reviewed journals on naturopathic therapeutic modalities and practices, with a substantial proportion being observational studies, including research using survey, interview, or focus group methods (n = 195; 16.2%), and reviews and meta-analyses (n = 297; 24.6%).

The *HTA* also provides a look at how naturopathy/naturopathic medicine is used by providing details of an international naturopathic practice survey, community clinic survey, and survey on naturopathic knowledge mobilization, as well as a look at the prevalence of use of naturopathic practice globally and the safety and cost-effectiveness of naturopathic practice.

SUMMARY

The interest in and use of naturopathy/naturopathic medicine is expanding rapidly. In order for the profession to truly take advantage of this growth, naturopaths/naturopathic doctors need to be aware of the tremendous body of research that is available and know how to incorporate it into practice. The time has come for the naturopathic profession to truly shine.

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Evidence-Based Practice Attitudes, Skills, and Usage Among Canadian Naturopathic Doctors: A Summary of the Evidence and Directions for the Future

Monique Aucoin,[1] BMSc ND, **Matthew J Leach,**[2] PhD,and **Kieran Cooley,**[3] BSc ND

ABSTRACT

Evidence-based practice (EBP) is a framework aimed at facilitating the delivery of best practice care. Despite documented benefits, many health professionals have expressed concerns about EBP. Naturopathic medicine has been cited as being in opposition to EBP; however, this is not supported by the evidence. In a recent cross-sectional Canadian survey of naturopathic doctors, respondents self-reported a moderate to high use of EBP and use of a range of sources of evidence to guide clinical decisions. Evidence-based practice skill was reported to be moderately high, and attitudes were predominantly positive. These findings are consistent with other research undertaken on the topic which has identified a shift towards embracing EBP. Canadian naturopathic doctors have indicated a high level of interest in improving their EBP skills, and we present an upcoming opportunity for skill development.

Key Words Naturopathic medicine; naturopathy; evidence-based medicine

INTRODUCTION

Evidence-based practice (EBP) is a framework aimed at facilitating the delivery of best practice care. The framework emerged out of empiricism and scientific worldviews mixed with real-world concerns that new research evidence was not being incorporated into clinical practice in a consistent and timely manner.[1] In fact, it has been observed that it can take approximately 17 years for new research findings to change clinical practice.[2]

Evidence-based practice, or its precursor term evidence-based medicine (EBM), can be defined as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients." It involves the incorporation of clinical expertise and patient preferences with the best available research evidence.[1] There is mounting evidence to suggest that the use of EBP is associated with improved patient outcomes and patient satisfaction, as well as reduced healthcare costs.[3,4] Despite these documented benefits, many health professionals, across a variety of fields, have expressed concerns about EBP[5] and the necessity for a renaissance to refocus on the need to provide useful evidence, context, and clinical expertise for optimal patient care. The objective of this article is to review the evidence related to the use of EBP within the naturopathic profession, highlighting the results of a recent Canadian survey of naturopathic doctors (NDs), and from there, discuss future opportunities.

Naturopathic medicine is a system of health care that combines modern scientific knowledge with natural and traditional therapeutic approaches. The profession is unified by an approach to care that is guided by a set of six principles. These include an awareness of the healing potential of nature, treatment of the root cause of disease and the person as a whole, the avoidance of harm, the role of the doctor as a teacher, and the importance of prevention. Naturopathic medicine is regulated in six Canadian provinces: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, and Nova Scotia.[6] Within Canada, the therapeutic approaches used by NDs include clinical nutrition, lifestyle counseling, acupuncture, botanical medicine, homeopathy, and physical medicine. Naturopathic doctors may use additional modalities in certain provinces, including prescribed substances (such as pharmaceuticals or bioidentical hormones) and intravenous therapy. In North America, naturopathic medicine has an established record of providing effective and safe,[7,8] cost-effective,[9] patient-centred and culturally appropriate[10] care. This holds true globally.[11]

Efforts to improve the use of evidence across many healthcare disciplines have been made in recent years. At the same time, there

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has been increasing attention around the interface of naturopathic principles with modern scientific evidence and the way these different sources of information guide clinical decision-making. This attention has largely stemmed from one perspective: that naturopathic medicine may be averse to EBP,[12] and NDs need to increase efforts to improve either EBP uptake or design.[13,14]

Criticisms regarding the interface between naturopathic medicine and EBP have largely come from members of other professions,[15] as well the mainstream media—who to date have been heavily critical of naturopathic medicine.[16] Additionally, a commentary put forth by members of the profession has called for the addition of a seventh principle related to critical analysis.[17] Logan et al. suggest this is a necessary addition to the existing principles in order to guide an increase in structured critical appraisal and EBP use among NDs. The publication reviews some of the history of naturopathic medicine in North America and highlights the presence of mistrust in scientific consensus, use of fad-like therapeutic approaches, medical misinformation, and a lack of critical appraisal.[17] The authors suggest that naturopathic medicine's history and emphasis on expert opinion have slowed its evolution into a contemporary mainstream profession. As in many other professions,[18] concerns about the need for increased EBP knowledge and skill among NDs are legitimate; however, the intimation that the profession is in *opposition* to EBP is not consistent with the published evidence on this topic.

CONTEXTUAL RESEARCH ON EBP IN NATUROPATHIC MEDICINE

Over the past several years, efforts have been undertaken to understand the role of EBP in the practice of naturopathic medicine as well as the attitudes towards EBP among members of the profession. In 2018, a survey of Canadian NDs was undertaken by the Naturopathy Special Interest Group of the Interdisciplinary Network of Complementary and Alternative Medicine Research (INCAM).[19] The primary purpose of the survey was to explore the level of ND participation in the conduct of research as well as interest in, need for, and barriers to participation. The survey queried the 201 respondents on their beliefs related to EBP, such as the importance of defining outcomes, the importance of critical evaluation, and the importance of using evidence to improve the delivery of clinical care. Respondents reported a high level of agreement, with 84% to 100% of participants supporting each statement. Although these results suggest favourable attitudes, they did not assess the use of EBP or the level of EBP skill possessed by participants. The survey was also limited by a relatively small sample size and the risk of selection bias, as individuals more interested in the conduct of research, as well as the use of EBP, may have been more likely to complete the survey.

INSIGHTS FROM RECENT RESEARCH

More recently, a large multi-national initiative was undertaken to gain insight into EBP engagement, preparedness, and perceptions among complementary medicine practitioners (the Evidence-Based Practice in Complementary Medicine [EPICENTRE] Project). One component of this project involved a national cross-sectional survey of Canadian NDs.[20] The invitation to participate was circulated early in 2020 through the newsletters of the provincial associations and the Canadian College of Naturopathic Medicine. Additionally, invitations were shared in virtual communities of practice. A total of 223 participants completed at least 20% of the survey and their data were included in the analysis.

Participants of the EPICENTRE-Canada study for the most part were aged 30 to 39 and female, had graduated within the past 10 years, and had been practicing naturopathic medicine for 16 to 30 hours per week. Further, most respondents held a naturopathic diploma/degree as their highest qualification and had practiced in a clinical setting with other complementary and alternative medicine providers, mostly in an urban location.

The survey used the validated Evidence Based Practice Attitude and Utilisation Survey (EBASE) to assess the frequency with which respondents engage in EBP activities, their self-reported level of skill, and their attitudes towards EBP.[21] The median EBP use subscore was in the moderate to high range, with the majority of participants reporting a high level of use of online search engines and online databases. In terms of the type of evidence used, most respondents reported high usage of traditional knowledge and published clinical evidence, and infrequent use of laboratory evidence and trial and error. Overall, 71% of participants reported that a moderate or large proportion of their clinical practice was based on evidence from clinical research—which is relatively higher than that previously reported by chiropractors, osteopaths, herbalists, and yoga therapists.[21-24]

With respect to EBP skill, the median subscore corresponded to a moderate level. The majority of respondents reported a moderate–high level of skill related to asking about, acquiring, and appraising evidence. By contrast, participants reported a low level of skill related to the conduct of research, which is not surprising given that the participants were mostly clinicians. It is noted that the survey assessed self-reported level of skill and that a test that objectively measured knowledge or skills may have been more accurate.

The median score on the attitude subscale corresponded to a predominantly favourable attitude towards EBP. A large majority of participants responded "agree" or "strongly agree" to statements about EBP being useful, helpful in guiding clinical decisions about patient care, and necessary in the practice of naturopathic medicine. Participants responded similarly to statements that EBP takes into account their clinical decision-making and patient preferences, indicating participants had a high level of understanding of the EBP framework.

The EBASE questionnaire also queried participants about barriers and enablers to EBP. At least two-thirds of participants identified lack of time and lack of evidence in naturopathic medicine as minor to moderate barriers. Furthermore, 40% to 60% of participants also identified lack of resources (such as online databases) and an insufficient level of EBP skills as barriers. With respect to enablers, access to the internet and free online databases were rated highly, as was the ability to download full-text journal articles.

QUALITATIVE RESEARCH

To date, there have been limited qualitative analyses of Canadian ND attitudes towards EBP. However, such research has been conducted at an international level. A recent qualitative study involving American NDs suggested that views of the profession towards EBP have transitioned recently "from hesitancy to cautious embrace."[25] While most participants reported a generally favourable perception of EBP, there was significant diversity of attitudes within the profession. This is consistent with findings from a recent Canadian survey.[20] Notwithstanding, other qualitative studies have revealed more cautious views among NDs.

In a 2011 study involving Australian naturopaths, participants expressed concerns that scientific evidence could undermine traditional knowledge.[26] More recently, a theme of needing to find a balance between traditional and scientific knowledge was identified in a study involving ND students and faculty members from North America and Australia.[27] The importance of finding a balance between different sources of information appears to be a critical consideration for NDs.

In a recent survey of Canadian NDs, participants reported a high level of use of diverse information sources, including clinical evidence, traditional evidence, and patient preference.[20] This ability to integrate and combine different sources of information is consistent with the framework of EBP. A commentary on the role of EBP in naturopathic medicine suggested that recent efforts aimed at "teaching and applying EBM while honoring the philosophical and empirical tradition of naturopathic medicine has served to strengthen the profession overall."[28]

While the findings from these aforementioned studies are promising, there is still room for improvement. A Canadian study undertaken in 2015 conducted focus groups with students undergoing medical, chiropractic, and naturopathic training in order to understand the development of perspectives related to pediatric vaccination.[29] Insights that emerged included the influences of both education and informal socialization as well as a pattern of "uncritical" acceptance of the views of respected or senior members of the profession. These findings suggest that opportunities to improve critical analysis, or a more structured approach to documenting and assessing traditional knowledge, may be warranted so that students and members of the profession are skilled at viewing information through a lens of weighing and evaluating alternate or conflicting sources of evidence.

DISCUSSION

The evidence to date points to a possible change in NDs' attitudes towards EBP over time. This has been noted in the qualitative studies. However, as the two Canadian quantitative studies were cross-sectional and took place within the span of two years, they do not shed light on the progression of attitudes over time. No studies have been conducted to assess other ways of knowing or approaches used by NDs in adopting knowledge within the clinical encounter.

At the Canadian College of Naturopathic Medicine, significant efforts have been made to increase the development of EBP skills in the curriculum; the college has also hosted an annual research day, showcasing the research of faculty and students for the past five years.[30] Courses teaching EBP skills have an established presence in the curriculum at naturopathic medical education institutions, and these skills have been incorporated into the core competencies of the profession. Members of the profession have spoken out publicly about the value of EBP, stating, for example, that "EBM is a wonderful tool, and is here to stay… its application will strengthen our profession and improve our clinical effectiveness."[28]

The are many arguments in favour of EBP; for instance, EBP promotes a spirit of inquiry and can facilitate increased consistency of care within and across professions.[31] Evidence-based practice also emphasizes the development of critical appraisal skills, which are important in navigating the scientific literature, where conflicting findings and biased results are frequently present.[32] It has been posited that EBP is a structured method for self-directed life-long learning[33] well-placed to address the inherent challenges of false attribution, recall bias, inconsistent follow-up and small sample sizes that can be associated with clinical experience alone.[34] Additionally, EBP can increase transparency and accountability of decision-making, increase healthcare efficiency and increase professional credibility.[35]

However, the use of scientific evidence in naturopathic medicine, and health care more generally, is not without limitations and criticisms. Often cited is the relative lack of clinical trials of naturopathic modalities, which could lead to undervaluing or underuse of these modalities if a rigid approach to EBP is used.[31,36] Randomized controlled trials (RCTs) are an important source of evidence in EBP; however, they have significant limitations. Clinical trials often aim to answer a clearly defined question and use narrow participant inclusion criteria to do so; however, this may exclude complex, multimorbid patients who are common in clinical practice, limiting the applicability and translatability of findings to individuals in the real world. It has been recognized that vulnerable populations, such as individuals with low income or who are part of minority groups, are often under-researched, resulting in evidence that does not adequately support decision-making in these populations, compounding health inequalities.[37] Furthermore, RCTs have limitations when used to study complex, multimodal, and individualized treatment approaches.[38] An important consideration related to EBP is the possibility of limiting the diversity of sources of knowledge and invalidating ways of knowing other than the RCT, such as history, theory, and philosophy[39]; however, it is noted that the framework of EBP includes a range of sources of evidence and that a number of concerns about EBP stem from misunderstanding its definition. When American NDs were asked to define EBM in a 2017 study, NDs who described it more broadly (such as including numerous sources of evidence) also expressed less hostile views towards EBP.[25] While scientific evidence and clinical experience both possess strengths and limitations, it has been proposed that EBP can be thought of as a blending of these sources of knowledge in a way that maximizes the merits of each.[34]

CONCLUSIONS AND FUTURE DIRECTIONS

An important consideration moving forward is finding ways to support Canadian NDs in developing EBP knowledge and skills in a way that is appropriate and tailored. In the EPICENTRE-Canada survey reported above, an overwhelming majority of Canadian NDs (93%) indicated that they were interested in improving the skills needed to incorporate EBP into their clinical practice. This may suggest that Canadian NDs both are interested in EBP and have insight into their EBP-related skill deficits.

Responding to this skill development opportunity, a team of researchers is currently undertaking an EBP continuing education (CE) project in Canada. Over the summer of 2021, the team will be completing a co-design process in which 18 Canadian NDs will attend focus groups and provide feedback on their needs, interests, and preferences for an EBP CE course. The team will then amalgamate this feedback, together with best practices in EBP education, to create a CE course that is tailored for Canadian NDs. The course will be offered through the CCNM continuing education department in the coming months. As part of the research project, the team will be asking course participants to complete questionnaires before and after the CE initiative in order to capture changes in skills, behaviours, and attitudes. These data will help further our understanding of the educational needs of NDs, as well as facilitate improvements in the course for subsequent delivery.

The role of evidence in the practice of naturopathic medicine in Canada is complex and evolving. Overall, there is evidence of a strong degree of acceptance and use, as well as interest in further opportunities for skill development, which we hope to facilitate.

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We have read and understood the *CAND Journal's* policy on conflicts of interest disclosure and declare the following interests: MA, KC, and ML are involved in the creation and delivery of continuing education on EBP skills for naturopathic doctors that may involve direct or indirect personal benefit.

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Hyperthermia in Cancer Care: A Literature Review

Ellen Conte,[1,2] **Athanasios Psihogios,**[1,2] and **Dugald Seely**[1,2]

ABSTRACT

Introduction: Hyperthermia (HT) in cancer management refers to the external application of heat to raise intratumoural temperature to between 39°C and 45°C. Locoregional hyperthermia (LRHT) is the most used and studied type of HT in cancer care. A literature search was conducted to produce a monograph to help clinicians and patients make informed choices in considering the application of this therapy.

Methods: A search was performed in Medline and Cochrane library for LRHT and cancer in May 2020. Eligible studies were English-language clinical studies reporting on efficacy, quality of life (QoL), safety, or feasibility. Additional cursory literature scoping was performed to identify missing papers and background information. Papers were independently screened by two reviewers. Following development of a full monograph, a condensed version suitable for publication was created and is presented here.

Results: A total of 980 articles were identified and 166 met inclusion criteria. Most were single-arm or observational. However, among the 166, there were 7 systematic reviews (including 37 RCTs) and 18 additional RCTs identified. Several mechanisms of action have been proposed for HT in cancer care including physiological changes, direct cytotoxic effects, chemosensitization and radiosensitization, and immune modulation. Locoregional HT is used primarily as an adjunct to chemotherapy and radiotherapy due to its possible synergistic effects. Various studies demonstrated improved outcomes for patients treated with LRHT and chemo-and/or-radiotherapy. The best evidence for improved disease control and survival is seen for breast cancer (locally recurrent), cervical cancer, esophageal and gastric cancers, head and neck squamous cell carcinoma, and high-risk soft tissue sarcoma. Research related to quality of life (QoL) is limited and often focuses on pain. Hyperthermia with modern technology and treatment planning is generally well tolerated; the most common side effects are discomfort, mild pain, local erythema, skin burns, and, less commonly, subcutaneous burns. Trial heterogeneity and methodological concerns limit the strength of conclusions.

Conclusions: Locoregional HT is a promising adjunct treatment to chemotherapy and radiotherapy for a variety of cancer types. To determine in what situations this therapy could be best applied, more high-quality well-controlled studies are needed.

Key Words Locoregional Hyperthermia, Oncothermia, Oncology, Integrative Oncology, Naturopathic Oncology

INTRODUCTION

Hyperthermia (HT) for cancer involves heating cells and tissue to temperatures above the normally maintained range via exogenous means to selectively affect tumours. It is usually used in combination with conventional care.[1] Several types of HT exist: local (LHT), regional (RHT), interstitial and endocavitary, whole-body, hyperthermic isolated limb perfusion,[2] hyperthermic intraperitoneal chemotherapy (HIPEC), and hyperthermic intravesical chemotherapy (HIVEC).[3] Local and regional hyperthermia (locoregional hyperthermia; LRHT) is available in a few Canadian naturopathic practices. Local HT increases the temperature of superficial tumours using applicators or antennae over skin with a contact medium.[3] In RHT, deep tumours and body regions are heated by arrays of antennas; often arranged in a ring around the patient.[2] The applicators typically emit microwaves or radio waves to heat the tumour.[2] Locoregional HT aims to increase intratumoural temperature to 39–45°C, although 41–43°C is considered optimal.[4,5]

Despite many LRHT studies for cancer care, no comprehensive resource outlining clinical evidence exists. Therefore, a detailed

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and structured literature search was performed to evaluate the clinical efficacy of LRHT in cancer care, from which a comprehensive monograph was developed, and its adapted condensed review presented here.

METHODS

Medline and Cochrane Library were searched in May 2020 without date restrictions. Search terms included the neoplasm medical subject headings (MeSH) terms, and terms related to LRHT, including: local hyperthermia, locoregional hyperthermia, regional hyperthermia, modulated electrohyperthermia, external hyperthermia, part-body hyperthermia, and oncothermia. Scoping and reference reviews were performed to identify additional papers. Titles and abstracts were screened in duplicate, followed by single-review of full-text publications (Figure 1).

Inclusion criteria included English-language studies of human populations with cancer receiving external LRHT. Studies could investigate outcomes related to clinical effectiveness (e.g., survival, recurrence, response), quality of life (QoL), safety, adverse events (AEs) and feasibility. Eligible study designs included systematic reviews and meta-analyses, clinical trials, and observational studies. Exclusion criteria included preclinical trials, narrative reviews, case studies, other types of HT, and/or technical studies on HT instrumentation. Studies accounted for in systematic reviews or meta-analyses were excluded to not be described twice.

This literature review is a condensed version derived from the full monograph for LRHT and cancer care. The cancers with the most available evidence are the focus of this condensed literature review. Studies of patients with mixed cancer types were omitted due to space limitations and heterogeneous participant samples, designs, and quality. Complete details can be found in the full monograph by contacting the corresponding author.

RESULTS

A total of 1,000 articles were identified. Scoping and reference review identified an additional 25 papers. After deduplication, 980 articles were screened, and 166 were included in the monograph (Figure 1). This condensed literature review, which does not discuss mixed cancer types, includes 126 papers.

Efficacy

Cancer types with the most rigorous research are described henceforth in detail. Systematic reviews and meta-analyses are described in Table 1, and randomized controlled trials (RCTs) in Table 2. Full discussion of all data identified in the original literature search can be found in the healthcare provider monograph; please contact the corresponding author for more information and access details.

Breast Cancer

One meta-analysis (31 articles reporting on 34 studies)[11] and two single-arm trials[31,32] were identified. The meta-analysis included five RCTs, three non-randomized controlled trials, and 26 single-arm trials, all of which investigated LRHT combined with radiation (RT) for locally recurrent breast cancer.[11] Based on

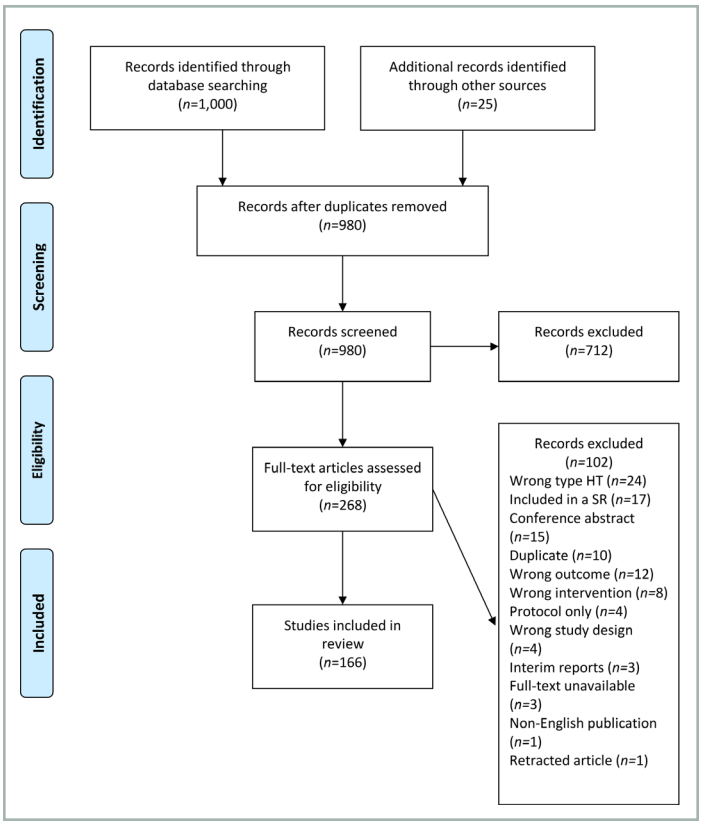

FIGURE 1 Prisma flow diagram. HT = hyperthermia; SR = systematic review.

controlled trials (both randomized and non-randomized) from the meta-analysis, the complete response (CR) rate was 60.2% in the combination group and 38.1% in the control group (odds ratio [OR]: 2.64; 95% confidence interval [CI]: 1.66–4.18, $p < 0.0001$). Based on single-arm trials, the CR rate was 63.4%. Mean acute and late grade III/IV toxicities were higher in the hyperthermia group compared with the control (14.4% vs 5.2%). As publication dates spanned 34 years, no uniform toxicity scoring criteria or review could be presented.

Two single-arm studies not included in the meta-analysis were identified.[31,32] The first reported jointly on two phase I studies including 29 patients with chest-wall recurrences, all of whom had received prior standard treatments.[31] Locoregional HT delivered within 30 to 60 minutes of doxorubicin resulted in a response rate of 48.3%, with 17.2% having CR. All adverse events (AEs) were reported as chemotherapy-related. The second single-arm trial ($n = 7$) applied chemotherapy and LRHT simultaneously for patients with recurrent, inoperable breast cancer who had received prior conventional care.[32] All participants experienced an objective response (OBJR), with four CR and three partial responses (PR). Median time to recurrence was six months.

Cervical Cancer

Two systematic reviews with meta-analysis[7,8] (reporting on seven RCTs), five publications on three RCTs,[19,20,28,29,33] and six single-arm trials were included.[34-39]

The latest systematic review, which performed two separate analyses (conventional and network meta-analysis) of LRHT for

TABLE 1 Systematic reviews and meta-analyses of locoregional hyperthermia (LRHT) for cancer

Reference	Study Design	# of Trials and Participants	Population	Intervention	Control	Results
Hu et al., 2017[6]	Systematic review and meta-analysis	19 RCTs (n=1,519)	Esophageal cancer – mixed staging	Hyperthermia chemo-radiotherapy (HCRT)	Chemo-radiotherapy (CRT) or radiotherapy (RT)	**HCRT vs CRT** *1-, 3-, 5-, 7-yr survival:* OR and 95% CI 1.79, (1.12–2.84, p=0.01), 1.91, (1.27–2.87, p=0.002), 9.99, (1.72–57.91, P=0. 01), and 9.49, (1.14–79.27, p=0.04) respectively. 2-yr survival was not statistically significantly different. *Complete response rate:* OR 2.00, (1.49, 2.69, p<0.00001) *Safety:* Decreased GI reactions, leukocytopenia, radiation-esophagitis (OR 0.43, 0.49, 0.43 respectively, p<0.0001) **HCRT vs RT** *1-, 2-, 3-, 5-yr survival:* OR and 95% CI 3.20 (2.07–4.95, p<0.00001), 2.09 (1.13–3.85, p=0 02), 2.43 (1.67–3.51, p<0.00001), 3.47, (1.08–11.17, p=0.04) *Complete response rate:* OR 2.12, (1.29, 3.47, p=0.003) *Safety:* No statistically significant differences; however, HCRT trended towards higher rates of GI reactions, leukocytopenia, and radiation oesophagitis and a trend towards lower rates of radiation pneumonitis.
Datta et al., 2016[7]	Systematic review and meta-analysis	Conventional meta-analysis: 6 RCTs (n=427) Network meta-analysis: 8 trials (7 RCTs, 1 meta-analysis, n=1,160)	Cervical cancer – locally advanced (stage IIb–IVa)	Hyperthermia radiotherapy (HTRT) and Hyperthermia chemotherapy radiotherapy (HCRT)	Radiotherapy (RT) and chemoradiotherapy (CRT)	***Conventional meta-analysis of HTRT vs RT*** *Complete response:* HTRT vs RT, OR 2.67 (95% CI 1.57-4.54, p<0.001), NNT 4.5 *Locoregional control:* HTRT vs RT, OR 2.61 (95% CI: 1.55–4.39, p<0.001), NNT 4.3 *Survival:* HTRT vs RT, OR 1.94 (95% CI 1.10–3.40, p=0.021) *Toxicities:* no significant differences in acute or late toxicities ***Network meta-analysis*** *Complete response:* HCRT was superior to CRT (OR 2.91, 95% CI 1.97–4.31) and RT (OR 4.52, 95% CI 1.93–11.78). *Survival:* HCRT was superior to CRT (OR 2.65, 95% CI 1.51–4.87) and RT (OR 5.57, 95% CI 1.22–23.42). Rankogram and SUCRA values showed the best option for response and survival was HCRT followed by HTRT.
Lutgens et al., 2010[8]	Systematic review and meta-analysis	6 RCTs (n=267)	Cervical cancer – locally advanced (stage 2b–4a) *Most had stage IIIb	Hyperthermia + radiotherapy (HTRT)	Radiotherapy (RT)	Combined HTRT had superior outcomes for: *Complete response:* RR 0.56, 95% CI 0.39–0.79, p<0.001 *Local recurrence rate:* RR 0.48, 95% CI 0.37–0.63, p<0.001 *OS:* HR 0.67, 95% CI 0.45–0.99, p = 0.05 *Toxicities:* no significant difference in acute or late toxicity between arms

TABLE 1 (cont'd)

Reference	Study Design	# of Trials and Participants	Population	Intervention	Control	Results
Van der Horst et al., 2018[9]	Systematic review	14 studies (n= 395); 8 studies used LRHT (n=189) None were RCTs, all were observational (8 retrospective, 6/14 included a control group)	Pancreatic cancer – locally advanced or metastatic	Hyperthermia (locoregional, whole body, intraoperative)	Radiotherapy and/or chemotherapy (Chemotherapy in 60%, chemo/rads in 33%, radiation alone in 7%)	*RR (11 studies):* 31.3% In 3/11 studies with a control group, response rate was 43.9% in HT group vs 35.3% in control group. *Survival (12 studies):* 10.5 months. For 6/12 studies with a control group, median OS was 11.7 months (6–18.6) in HT group, vs 5.6 for control group (4–11). *Safety:* The only severe hyperthermia-related AE was subcutaneous fatty burn in one patient receiving intraoperative hyperthermia. *Note:* Full meta-analysis was not done due to quality of studies. These results were not exclusive for LRHT, but combined multiple types of HT
Datta et al., 2016[10]	Systematic review and meta-analysis	6 studies: 5 RCTs, 1 non-randomized controlled trial (n=451)	Head and neck squamous cell carcinoma – mostly stage III/IV	Hyperthermia + radiotherapy (HTRT) (locoregional in 5/6, intracavitary in 1/6)	Radiotherapy (RT)	***Complete response*** *RT alone:* 39.5%, *HTRT:* 62.5%, OR 2.92 (95% CI: 1.58–5.42, p=0.001) The corresponding risk reduction was 1.61 (95% CI: 1.32– 1.97, p=0.0001, I^2 = 13.37, p=0.329) and risk difference 0.25 (95% CI: 0.12–0.39, p=0.0001, I^2 = 59.44, p=0.031). No increase in toxicities with HTRT compared with RT alone.
Datta et al., 2015[11]	Systematic review and meta-analysis	31 papers (reporting on 34 studies); 6 single-arm studies, 5 RCTs, 3 non-randomized controlled (n=1,792)	Breast cancer - Local/regional recurrence	Hyperthermia + radiotherapy (HTRT) HT most often applied 2x/week following radiation, mean temperature 42.5 °C	Radiotherapy (RT)	***Controlled clinical trials*** *Mean complete response rate:* *HTRT:* 60.2% vs Radiotherapy: 38.1% (OR: 2.64; 95% CI: 1.66-4.18, p<0.0001) *Single-arm studies:* HT group complete response: 63.4% (event rate 0.64; 95% CI: 0.57–0.66)
Longo et al., 2016[12]	Systematic review	16 studies; 8 single-arm trials, 1 RCT, 1 non-randomized trial, and 6 observational studies (4 retrospective, 2 prospective) (n=346)	Bladder cancer – mix of muscular-invasive and non-muscular invasive	Hyperthermia with chemotherapy and/or radiation and/or surgery Temperature range 38–45.5°C	Mixed conventional care alone	RFS at 24 months was reported in 2 single-arm trials: 78% and 33%, respectively. *CR rate:* (one non-randomized controlled clinical trial): 54.5% in HT group vs 35% in the control group (p value not provided) *OS:* (one RCT) not significantly different between groups (28% vs 22%, p>0.05)

RCT = randomized controlled trial; HCRT = hyperthermia chemotherapy radiotherapy; CRT = chemoradiotherapy; RT = radiation; OR = odds ration; CI = confidence interval; GI = gastrointestinal; HTRT = hyperthermia radiotherapy; NNT = number needed to treat; SUCRA = surface under the cumulative ranking curve; OS = overall survival; RR = response rate; HT = hyperthermia; AE = adverse event.

patients with locally advanced cervical cancer, was published in 2016.[7] In the conventional meta-analysis conducted (6 RCTs, n = 427), HT with radiotherapy (HTRT) was found to outperform RT for CR (OR 2.67, 95% CI 1.57–4.54, p < 0.001) and long-term locoregional control (OR 2.61, 95% CI: 1.55–4.39, p < 0.001). Overall survival (OS) was superior in the HTRT group compared with RT (OR 1.94, 95% CI 1.10–3.40, p = 0.021). However, risk difference was not significant (8.4% difference, p = 0.299). In the network meta-analysis conducted (7 RCTs, n = 1,160), HT combined with chemotherapy and radiation (HTCTRT) was superior to chemotherapy combined with radiation (CRT) (OR 2.91, 95% CI 1.97–4.31), and RT (OR 4.52, 95% CI 1.93–11.78) for CR. The OS in the HTCTRT group was superior to chemoradiotherapy (CRT) (OR 2.65, 95% CI 1.51–4.87) and RT (OR 5.57, 95% CI 1.22–23.42). A 2010 Cochrane review found similar results.[8]

Three controlled trials yielded five publications since the last systematic review.[19,20,28,29,33] One multicentre RCT (n = 101) that included treatment-naive patients with locally advanced cervical cancer reported that the addition of LRHT to CRT did not improve overall five-year survival (adjusted hazard ratio [HR]: 0.485, 95% CI: 0.217–1.082, p = 0.077), disease-free survival (DFS) (adjusted HR: 0.517, 95% CI: 0.251–1.065, p = 0.073), local relapse-free survival (LRFS) (p > 0.05) or CR (p > 0.05) compared with CRT alone.[20]

TABLE 2 Randomized controlled trials of locoregional hyperthermia (LRHT) for cancer

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Issels et al., 2010[13]	Multicentre phase III, open label RCT, (EORTC 62961-ESHO 95 Trial)	*N*=341 (Tx 169, control 172) **Soft-tissue sarcoma (STS)** – adults with localized STS (tumour 5 cm or greater, FNCLCC grade 2 or 3, no distant metastasis)	Chemotherapy + regional HT Neoadjuvant chemotherapy x 4 (doxorubicin, ifosfamide, etoposide) with HT (60 minutes targeting 42°C) day 1 and 4 of 21-day cycle followed by surgery or radiation, and another 4 cycles of adjuvant chemotherapy + HT	Neoadjuvant and adjuvant chemotherapy alone (doxorubicin, ifosfamide, etoposide)	Primary outcome: local PFS Secondary outcomes: DFS, OS, tumour response, toxicity Follow-up was 5+ years	***Local PFS*** HT group less likely to progress than control group, relative hazard 0.58, (95% CI 0.41–0.83, p=0.003) Absolute difference at 2 years of 15% (95% CI 6–26, 76% HT vs 61% control) ***Secondary outcomes*** *DFS:* Relative hazard 0.70 (95% CI 0.54–0.92, p=0.011) for Tx compared with control *Tx response rate:* 28.8% Tx group, 12.7% control group (p=0.002). *OS:* was better in Tx group (HR 0.66, 95% CI 0.45 – 0.98), p=0.038 *Toxicity:* HT-related AEs: mostly mild to moderate (less than 5% severe): pain, bolus pressure, skin burn. Increased leucopenia in Tx arm vs control arm (77.6% vs 63%, p=0.005)
Angele et al., 2014[14]	Subgroup analysis of (EORTC 62961 –ESHO 95 Trial) Phase III, multicentre, open-label RCT	*N*=149 (subgroup of the total 341-person population) **Soft-tissue sarcoma (STS)** – adults with abdominal or retroperitoneal high-risk sarcoma, who had macroscopic complete resection (R0, R1).	Chemotherapy + regional HT Neoadjuvant chemotherapy x 4 (doxorubicin, ifosfamide, etoposide) with HT (60 minutes targeting 42°C) day 1 and 4 of 21-day cycle followed by surgery or radiation, and another 4 cycles of adjuvant chemotherapy + HT	Neoadjuvant and adjuvant chemotherapy alone (doxorubicin, ifosfamide, etoposide)	Local PFS, DFS, OS after 5-year follow-up	*Local PFS:* 56% in Tx arm vs 34% in control arm (p=0.044) *DFS:* 34% in Tx arm vs 27% in control arm (p=0.04) *OS:* no difference between groups (57% vs 55% in Tx vs control)
Issels et al., 2018[15]	Long-term outcomes of the EORTC 62961 – ESHO 95 Trial Phase III, multicentre, open-label RCT	*N*=341 (Tx 169, control 172) **Soft-tissue sarcoma (STS)** – adults with localized STS (tumour 5 cm or greater, FNCLCC grade 2 or 3, no distant metastasis)	Chemotherapy + regional HT Neoadjuvant chemotherapy x 4 (doxorubicin, ifosfamide, etoposide) with HT (60 minutes targeting 42°C) day 1 and 4 of 21-day cycle followed by surgery or radiation, and another 4 cycles of adjuvant chemotherapy + HT	Neoadjuvant and adjuvant chemotherapy alone (doxorubicin, ifosfamide, etoposide)	Primary: local PFS. Secondary: OS At a median follow up of 11.3 years	*PFS:* improved in Tx arm, HR 0.65 (95% CI 0.49–0.86, p=0.002) *OS:* HR 0.73 (95% CI 0.54–0.98, p=0.04) with 5-yr survival of 62.7% vs 51.3%, and 10-yr survival or 52.6% vs 42.7%. Absolute differences in survival at 5 and 10 years were 11.4% and 9.9%, respectively. Both differences reported to be statistically significant (p<0.05)

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Fang et al., 2019[16]	RCT	*N*=118 (55 in Tx, 63 in control) **Gastric cancer** – stage III/IV	Regional HT + chemotherapy (HTCT). Chemotherapy was a 3-week cycle of IV oxaliplatin and oral S1. HT was administered twice weekly (60 minutes, target temperature 42–43°C) from start to end of chemotherapy.	Chemotherapy alone	ORR (CR + PR) Disease control rate (DCR) (CR, PR, SD) OS Safety	*Disease control rate:* 70.9% and 46.0% for HTCT and control groups respectively (p=0.006) *mOS:* 23.5 months for HTCT group and 14 months for control (p=0.01) *3-yr survival rate:* RHCT 11.4%, control 0% (p=0.018) *Safety:* No difference in grade 3/4 AEs ORR was not reported on in the study; however, from looking at the table, it appears there was no difference as no one experienced a complete response
Guo et al., 2007[17]	RCT	*N*=18 (9 in Tx, 9 in control) **Metastatic melanoma** – refractory to other treatments, with an accessible tumour mass	Local HT + intratumoural dendritic cell (DC) injections HT administered for 1 hour prior to DC injection (42–43°C), 3x in week 1 of a 28-day cycle, up to 2 cycles administered	Intratumoural injection of dendritic cells (DC) alone	ORR (CR + PR) and DCR (CR + PR + SD) Time to progression (TTP) Survival Toxicity Melanoma-specific antitumour immunity	***DC Response*** 77.8% in Tx arm, 44.4% in control arm, p<0.05. *Tx arm:* 1 CR, 3 PR, and 3 SD. *Control arm:* 1 PR and 3 SD. *TTP:* 5 months and 2 months Tx and control arm respectively (p<0.05) *Median survival:* No significant difference (13 months vs 6 months, p>0.05). *Safety:* 42 AEs in Tx arm, 19 AEs in control arm. Grade 1/2 lymphopenia was the most common AE in treatment arm, other AEs included: sweating, vomiting, malaise, which all recovered within 24–48 hours. *Antitumour immunity:* Cell assays demonstrated some possible anti-tumour immune effects of LHT: induction of cytotoxic T lymphocytes, heat shock protein expression, enhanced Th1/Th2 chemokine production, promoted migration of DC to afferent LNs.
Overgaard et al., 1995[18]	RCT	*N*=70 (134 malignant lesions) **Melanoma –** recurrent or metastatic melanoma lesions	Radiation + HT 3 fractions of radiation over 8 days, followed by 1-hour HT at target temperature of 43°C	Radiation alone	CR (at 3 months) Persistent local control Safety	*CR:* 62% in Tx arm, 35% in control arm (p<0.05) *2-yr local tumour control:* 28% in radiation alone vs 46% in combined treatment (p=0.008) Most important prognostic variables: hyperthermia (OR 2-yr local control: 1.73, 95% CI 1.07–2.78, p=0.023), radiation dose, tumour size. *Safety:* Addition of heat did not increase acute or late effects of radiation.

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Minnaar et al., 2019[19]	Phase III RCT, preliminary results	*N*=202 (101 in mEHT, 101 in control) **Cervical cancer** – FIGO stages IIB to IIIB SCC, treatment naïve. Patients recruited from a low-resource setting, and could be HIV+ or negative.	Modulated electrohyperthermia (mEHT) + chemo-radiotherapy (cisplatin) mEHT administered 2x/week immediately before radiation, to the pelvis, at a temperature of 42.5°C for a minimum of 55 minutes.	Chemo-radiotherapy alone	Primary: local disease control (at 6 months) Secondary: Toxicity (CTCAE) QoL Survival	*Local disease control:* higher in mEHT group (*n*=40, 45.5%) compared with control (*n*=2, 24.1%), *p*=0.003 *Local DFS*: mEHT group, *n*=39 (38.6%), control *n*=20 (19.8%), *p*=0.003 *Toxicity:* mEHT did not affect frequency of CRT-related early toxicities. Tx was well tolerated; 11 mEHT participants reported AEs: grade 1–2 adipose tissue burns, grade 1 surface burns. *QoL:* at 3 months post-Tx, fatigue and pain were reduced in the mEHT group and there was significant improvement in social function, emotional function. No differences between groups while on treatment.
Harima et al., 20016[20]	Multicentre, open-label, RCT	*N*=101 (50 control, 51 Tx) **Cervical cancer** – stage IIA–IVA, treatment naïve	HT + chemoradiotherapy Whole-pelvis hyperthermia (43°C) delivered once weekly concurrently with cisplatin + radiotherapy for 60 minutes, delivered for the duration of 3–5 chemoradiotherapy cycles	Chemoradiotherapy alone (cisplatin)	5-year survival, response rate, DFS, LRFS, AE/toxicity	*Overall 5-year survival:* No significant difference between HT group (77.8%) and control (64.8%). *p*=0.077). *DFS:* Not significantly different between both groups (*p*=0.183), with adjusted HR also showing no significant difference (*p*=0.73). *LRFS:* No significant difference between groups *Complete response:* No significant difference between groups. Adjusted complete response rate showed a significant difference (*p*=0.047) AEs were similar between groups
Mitsumori et al., 2007[21]	Multicentre, open-label, RCT	*N*=80 (40 control., 40 Tx) **NSCLC:** Locally advanced, stage II–III	HT + radiation HT delivered for 60 minutes/ session, once a week (minimum 5 sessions), in addition to radiation	Radiation alone	Survival, response, PFS, toxicity	*1-yr local PFS:* Significantly higher in the HT group (67.5%) compared with control (29.0%) (*p*=0.036). *1-yr OS:* Not significantly different between groups (*p*=0.868).
Shen et al., 2011[22]	Phase II RCT	*N*=80 (40 control., 40 Tx) **NSCLC:** advanced, stage IIIB–IV	HT + chemotherapy One hour after chemotherapy (cisplatin + gemcitabine), patients received HT (300–1,100 W), for 60 minutes, 2x/week. Target temperature 39–42.5 °C.	Gemcitabine + cisplatin, without HT	Tumour response, toxicity/AE, QoL, Clinical Benefit Response (CBR)	*Response rate:* No significant difference between groups *Global QoL:* HT group significantly improved compared with control; however, no differences among specific components
Shchepotin et al., 1994[23]	Three-armed RCT	*N*=293 – Surgery alone = 100 – Radiotherapy + Surgery = 98 – Surgery + Radiotherapy + HT = 95 **Gastric cancer:** non-metastatic	HT + radiation HT was delivered 2 hours after radiation, for 60–70 minutes, every day for 4 consecutive days prior to surgery (pre-operative phase). Tumour temperature target >42°C.	Surgery alone or surgery + radiation therapy alone	Survival	***3- or 5-year survival*** Hyperthermia + radiation did not significantly improve either compared with radiation alone. Compared with surgery alone, radiation + hyperthermia significantly improved 5-yr survival *p*<0.05.

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Petrovics et al., 2016[24]	RCT Pilot Study	*N*=50 (25 Tx, 25 control.) Mix of cancer types – all patients suffering from chronic fatigue syndrome	HT + Biobran (MGN-3-arabinoxylane) HT delivered 1x/week for 15 weeks. Unclear whether they also received standard care	Standard care (chemotherapy and radiation)	QoL, fatigue	*Whole-body pH*: Compared with baseline, HT group is reported to have significantly normalized whole body pH ($p<0.01$) *Antioxidant status:* significantly improved compared to baseline in HT group ($p<0.01$). *Fatigue:* significantly improved in the HT group ($p<0.01$), with no change noted in control group.
Pang et al., 2017[25]	Phase II RCT	*N*=260 (Tx: 130, control: 130) **Mixed peritoneal cancers:** stage III–IV with the presence of malignant ascites	HT + TCM herbal medicine HT was 60 minutes, every second day for 4 weeks (14 total sessions)	Standard intraperitoneal chemotherapy	Response, QoL, pain	*Objective response (CR + PR):* Significantly higher in the Tx group (77.69%) compared with control (63.85%) $p=0.005$. A non-significant benefit was noted for complete response in the Tx group compared with control. *KPS score:* significantly improved in Tx group compared with control $p<0.05$. *Adverse events:* occurred significantly more in the control group (16 cases) compared with Tx group (3 cases) $p<0.05$
Ou et al., 2017[26]	Phase I RCT	*N*=15 (5 in each arm) **NSCLC:** stage III–IV, all receiving standard treatment within the past 6 months	HT + IVC HT 3x/weeks for 4 weeks (60 minutes at 40–42°C), before, during, or after IVC	All three arms received HT; however, timing of IVC varied (prior, during, or after HT)	QoL, AE	*QoL:* the only measure that significantly improved compared with baseline was physical functioning. No significant between-group QoL differences/changes were found.
Ou et al., 2020[27]	Phase II RCT	*N*=97 (Tx: 49, control: 48) **NSCLC:** stage IIIb–IV, heavily pre-treated and refractory to prior Tx	HT + IVC + basic supportive care HT 3x/week (60 minutes, 40–42°C), simultaneous to IVC (1g/kg), 3x/week.	Basic supportive care alone	Response, PFS, DCR, survival, AE, QoL	*Median OS:*9.4 months in Tx group compared with 5.6 months in control (HR: 0.33, 95% CI: 0.16–0.41, $p<0.0001$. *Median PFS:* 3 months in Tx group compared with 1.85 months in control (HR: 0.33; 95% CI: 0.12–0.32, $p<0.0001$). *3-month disease control rate:* 42.9% in Tx group compared with 16.7% in control ($p=0.0073$). *QoL:* physical, emotional, and global improvements were significantly better in Tx group. Significant improvements were noted for symptoms such as fatigue, pain, nausea, SOB and appetite loss in the Tx group compared with control. *Biomarker changes:* no significant changes observed
Minnaar et al., 2020[28]	Phase III RCT	*N*=206 (control: 101, Tx: 105) **Cervical cancer:** stage IIB–III, HIV positive (CD4+ count > 200)	HT + radiation + cisplatin Immediately before radiation, patient received HT for 55 minutes, 2x/week. Patients also received cisplatin.	Radiation + cisplatin alone	Toxicity, QoL	*QoL:* At the 6-week mark, cognitive function was significantly higher in the HT group compared with control. At the 3-month mark, fatigue and pain were significantly reduced in the HT group. At the 3-month mark, compared with baseline, social functioning significantly improved.

TABLE 2 (cont'd)

Reference	Study design	Participants	Intervention	Control	Outcomes and measures	Results
Minnaar, et al., 2020[29]	Phase III RCT *Sub-analysis of Minnaar et al., 2020[28]	*N*=108 (Tx: 54, control: 54) **Cervical Cancer:** Tx group: 25 HIV+, 29 HIV–; control group: 26 HIV+, HIV– Participants included in this sub-analysis if they had nodes outside the treatment field and were evaluated 6 months post-treatment	HT + radiation + cisplatin Immediately before radiation, patient received HT for 55 minutes, 2x/week. Patients also received cisplatin.	Radiation + cisplatin alone	Evidence of an abscopal effect (based on complete metabolic resolution)	Evidence of complete metabolic response (CMR) was significantly higher in the HT group (24.1%) compared with control (5.6%) (p=0.013).
Van der Zee et al., 2000[30]	Multicentre RCT	*N*=358 (control: 176, Tx: 182) **Mixed Cancer:** bladder cancer (T2–T4, N0, M0), cervical cancer (stage IIB–IV) or rectal cancer (M0–1)	HT + RT HT 1x/week, 1–4 hours post radiotherapy (total of 5 Tx). Target temperature 42°C.	Radiation alone	Response, local control, survival	*Complete response:* Pooled analysis indicated that this was significantly higher in the HT group compared with control (58 vs 37%, respectively, p=0.003). Patients with cervical cancer and bladder cancer had significantly better CR rates than control (26% and 22%, respectively, p=0.003 and p=0.01, respectively). No significant difference was noted for rectal cancer. Patients with less advanced disease had better response than those with higher tumour stages (p=0.007). *Adjusted duration of local control:* Improved more in the intervention arm (p=0.01) *Survival:* Mean odds of mortality between groups was not significantly different (p=0.16). At 3-yr follow up, only patients with cervical cancer had a significantly better OS (51% vs 27%, p=0.009).

RCT = randomized controlled trial; EORTC = European Organisation for Research and Treatment of Cancer; ESHO = European Society of Hyperthermic Oncology; NNT = number needed to treat; CI = confidence intervals; STS = soft-tissue sarcoma; Tx = treatment; FNCLCC = French Federation of Cancer Centers Sarcoma Group; HT = hyperthermia; PFS = progression-free survival; DFS = disease-free survival; LRFS = local recurrence-free survival; OS = overall survival; mOS = median overall survival; AE = adverse event; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RHCT = regional hyperthermia and chemotherapy; TTP = time to progression; LHT = local hyperthermia; DC = dendritic cell; DCR = disease control rate; LN = lymph node; CRT = chemoradiotherapy; HTRT = hyperthermia radiotherapy; HCRT = hyperthermia chemoradiotherapy; mEHT = modulated electrohyperthermia; FIGO = International Federation of Gynecology and Obstetrics; SCC = squamous cell carcinoma; LRHT = locoregional hyperthermia; RT = radiotherapy; QoL = quality of life; HR = hazard ratio; OR = odds ratio; NSCLC = Non-small cell lung cancer; TCM = traditional Chinese medicine; IVC = intravenous vitamin C; KPS = Karnofsky performance status; SOB = shortness of breath.

Three papers published data from an ongoing phase III RCT investigating modulated electro-hyperthermia (mEHT) with CRT, compared with CRT alone, for patients with stage IIB–IIIB cervical cancer.[19,28,29] Patients from a low-resource African setting were treated with mEHT twice weekly before RT in addition to cisplatin-chemotherapy. The first publication reported early results.[19] At six months, the local disease control and local DFS were superior in the mEHT group than in the control (45.5% vs 24.1%, p = 0.003; 38.6% vs 19.8%, p = 0.003, respectively). The second publication found no significant difference in treatment toxicity between study arms, and AEs attributed to mEHT were minor.[29] There was some evidence of QoL improvement, specifically for cognitive function, post-treatment fatigue, and social and emotional functioning in the HT arm. The third publication evaluated the abscopal effect in a subgroup of patients with involved lymph nodes outside of the treatment field.[28] Participants in the LRHT arm experienced significantly higher complete metabolic response (abscopal effect marker) than the control (24.1% vs 5.6%, p = 0.013).

Lastly, a controlled clinical trial in patients with recurrent, previously irradiated cervical cancer administered platinum-based chemotherapy with (n = 18) or without (n = 20) mEHT.[33] Objective response rates were superior in the mEHT group than in the control (p = 0.046). However, there was no significant OS difference.

Six phase I and II studies were identified.[34-39] Four phase I/II studies evaluated LRHT administered with cisplatin in patients with pelvic recurrences.[34,36,38,39] The first study found that LRHT alongside six-weekly cisplatin treatments in 19 patients produced

an overall response rate of 53% with no dose-limiting toxicities.[34] An additional 28 people were enrolled and the full dataset of 47 people was published separately.[38] The OBJR rate from that publication was 58%, with a median OS of eight months. In patients with pain, 74% achieved palliation. A phase II study administered LRHT simultaneously with cisplatin in 23 patients.[36] The response rate was 52%, median duration of response 9.5 months, mean OS 8 months, and one-year survival 42%. Another phase I/II study in patients with treatment-naive stage IIB–IVA cervical cancer published early[39] and late results.[37] Sixty-eight people were treated with RT, weekly cisplatin, and four weekly-whole pelvis LRHT treatments. Complete response was observed in 90% of patients. Two-year DFS and OS were 71.6% and 78.5%, respectively, and five-year DFS and OS were 57.5% and 66.1%, respectively. Lastly, a phase II study administered LRHT to 18 patients with advanced cervical cancer receiving 28-fractions of RT.[35] Thirteen patients had a CR, four patients a partial response, and there was a local control rate of 48% at two years.

Esophageal Cancer

One meta-analysis (19 RCTs),[6] two single-arm trials,[40,41] and one observational trial[42] were identified. The meta-analysis (n = 1,519) published in 2017 compared HTCTRT with CRT and RT.[6] Compared with CRT, HTCTRT significantly improved one-year survival (OR 1.79, 95% CI 1.12–2.84, p = 0.01), three-, five-, and seven-year survival, but not two-year survival. In terms of response rate, HTCTRT significantly improved the rate compared with CRT alone (OR 2.00, 95% CI 1.49–2.69, $p < 0.00001$) but did not significantly alter recurrence or distant metastasis rates. HTCTRT decreased several adverse effects of CRT, including gastrointestinal reactions, leukocytopenia, and esophagitis. When comparing HTCTRT with RT, HTCTRT significantly improved one-year survival (OR 3.2, 95% CI 2.07–4.95, $p < 0.00001$) and survival at two, three, and five years. Quality of the individual RCTs was generally low.

Two single-arm studies[40,41] and one observational study[42] were also reviewed. The phase I/II study evaluated feasibility and toxicity of combined chemotherapy and LRHT for patients with esophageal cancer.[41] Locoregional HT administered on day 1 of neoadjuvant chemotherapy was feasible with acceptable toxicity. Another phase II study enrolled 28 people with resectable esophageal cancer and applied neoadjuvant CRT with LRHT.[40] The response rate was 74%, with 19% having a CR. After a median follow-up of 37 months, locoregional disease control was 100%, one-year, two-year, and three-year survival were 79%, 57%, and 54%, respectively. Lastly, one retrospective observational study evaluated combined radiotherapy and LRHT with or without cisplatin to patients with supraclavicular lymph node metastasis.[42] The three-year progression-free survival (PFS) and OS were 34.9% and 42.5%, respectively.

Gastric Cancer

Two RCTs,[16,23] one single-arm study,[43] and two observational studies[44,45] were identified.

A phase II RCT (n = 118) enrolled patients with advanced gastric cancer who received chemotherapy with or without LRHT twice per week.[16] For the HCT group compared with the chemotherapy group, the disease control rate (CR/PR/Stable Disease) was 70.9% vs 46.0% (p = 0.006), mean OS was 23.5 months vs 14 months (p = 0.01), and the three-year survival rate was 11.4% vs 0% (p = 0.018). There were no group differences in grade III/IV AEs.

Another large (n = 293) three-armed RCT randomized patients with newly diagnosed non-metastatic gastric cancer to surgery alone, preoperative RT, or preoperative HTRT.[23] Compared with surgery alone, HTRT significantly improved three-year survival (57.6% ± 6.3 vs 35.5% ± 4.9, $p < 0.05$) and five-year survival (51.4% ± 6.6 vs 30.1 % ± 4.7, $p < 0.05$). Radiotherapy alone did not significantly improve survival compared with surgery alone. There was no significant difference between survival for the RT group and the HTRT group, indicating no advantage of adding HT.[23]

The small single-arm study evaluated LRHT in 25 patients with unresectable, recurrent gastric cancer.[43] Amongst nine patients who had peritoneal carcinomatosis treated with LRHT, the survival outcomes were superior to a historical comparator (12.8±8.6 months vs 6.4±5.0 months, $p < 0.01$), but poor design and reporting limit generalizability.

One of the observational studies (retrospective) administered regional abdominal LRHT during intraperitoneal cisplatin for patients with stage IIA–IIIC surgically resected gastric cancer who were also receiving IV 5FU and leucovorin.[44] After 58 months, 68.2% recurred and 45.5% had died. Lastly, the other retrospective study evaluated a multimodal intervention of chemotherapy, ketogenic diet, insulin induced hypoglycemia, hyperbaric oxygen therapy (HBOT), and mEHS in patients (n = 25) with stage III/IV gastric cancer.[45] The treatment was administered in a three-week cycle of chemotherapy with HT and HBOT given sequentially for 60 minutes each on the day of, or day after, chemotherapy. The CR rate was 88%, mean OS 39.5 months (95% CI 28.1–51.0), and mean PFS was 36.5 months (95% CI: 25.7–47.2). There were no AEs attributed to the ketogenic diet, mEHT, or HBOT.

Head and Neck Squamous Cell Carcinoma

One systematic review and meta-analysis[10] (six controlled trials), one non-randomized controlled trial,[46] five single-arm clinical trials,[47-51] and three observational studies[52-54] were identified. The 2016 systematic review and meta-analysis of LRHT with RT for primarily locally-advanced head and neck cancer (HNC) reviewed six studies (five RCTs).[10] One study used intracavitary HT, which is outside the scope of this review. However, it does not appear that the findings would significantly skew the results. The CR rate of RT alone was 39.6% compared with 62.5% with HTRT (OR 2.92, 95% CI 1.58–5.42, p = 0.001). The risk difference was 0.25 (95% CI 0.12–0.39, $p < 0.0001$). Funnel plots indicated no publication bias. However, there were a small number of studies included. Rates of grade III/IV toxicities were similar between groups.

Two single-arm studies evaluated LRHT with RT for HNC. One of the phase I/II studies delivered LRHT and RT to 27 patients with cervical lymph node metastasis.[47] The response rate was 92%, and the five-year nodal control and survival were 64.5% ± 19%, and 24% ± 10%, respectively. The other phase I/II single-arm

trial[48] included 13 participants with parotid cancer and administered HTRT. Complete response was observed in 16/20 lesions and PR in the remaining four.

Three single-arm trials and one observational study evaluated combined LRHT and CRT.[49,50,52,55] All three trials administered radiation five times per week with weekly chemotherapy and twice weekly LRHT. In one study, 53 patients with HNC with N2 or N3 metastatic cervical lymph nodes were treated.[49] The local CR rate was 82% and the PR rate 9%; the nodal CR rate was 85% and the PR rate 9%. At two years, the OS and DFS were 51% ± 9% and 54% ± 8%. Treatment toxicity was deemed acceptable. In the second study, 20 patients with previously treated recurrent metastatic cervical LNs were included.[50] Symptom palliation (pain, bleeding, difficulty breathing, difficulty swallowing, difficulty speaking) occurred in 19/20 patients. Response rates included 8/20 with a CR and 11/21 with a PR. The one-year OS was 39% ± 11%, with three patients alive at three years. Adverse events were generally grade 1 to 2 hematological and skin toxicity. A retrospective analysis of 40 patients with advanced HNC given seven weeks of radiation and once weekly LRHT and chemotherapy reported CR and PR rates of 76.23% and 23.68%, respectively, and one-year and two-year OS of 75.69% and 63.08%, respectively.[52]

Three small studies evaluated LRHT with chemotherapy.[46,51,54] A non-randomized controlled trial administered chemotherapy alone or with LRHT for patients with nodal-metastatic HNC.[46] The overall tumour response rate was 36% in the control group, compared with 100% in the intervention group (no statistics presented). In another study (pilot), eight patients with advanced or recurrent disease were treated with carboplatin plus LRHT once every four weeks for 1 to 3 rounds.[51] There was one CR and two PRs. Six patients died within 4 to 13 months, with two long-term survivors. The last study (n = 31) included patients with local squamous cell carcinoma (SCC) of the lip treated with twice weekly IV bleomycin and methotrexate, followed by HT for 4.5 to 7.5 weeks, reporting a CR and PR rate of 93.55% and 6.45%, respectively.[54] Among those experiencing CR, during a five-year follow-up there was one local recurrence and one death. Authors noted good cosmetic results.

Lastly, a small retrospective analysis evaluated LRHT with radiation and cetuximab.[53] Six patients with locally advanced SCC were treated with radiation for six to seven weeks, with once weekly cetuximab and LRHT. All patients experienced a CR; side effects included mucositis and acneiform rash.

High-Risk Soft-Tissue Sarcoma (STS)

One RCT (yielding three publications),[13-15] five observational studies[56-60], and seven single-arm trials[61-67] were identified. Additionally, one single-arm trial[68] included deep seated sarcomas, and one observational study mixed soft tissue tumours.[69]

The RCT (multicentre), which included patients with localized, high-risk soft-tissue sarcoma (STS), found the addition of regional HT enhanced the effect of chemotherapy.[13] Participants (n = 341) were randomized to receive four three-week cycles of chemotherapy with or without HT (days 1 and 4). Following surgery and/or radiation, patients received another four cycles of their allocated treatment. The first publication from this trial reported that after a 34-month median follow-up, the HT arm had superior PFS (HR 0.58, 95% CI 0.41–0.83, p = 0.003) and an absolute difference in PFS of 15% at two years (CI 6%–26%). Disease-free survival (HR 0.70, 95% CI 0.54–0.92), treatment response rate (28.8% vs 12.7%, p = 0.002), and OS (HR 0.66, 95% CI 0.45–0.98) were also improved in the regional HT arm compared with the control arm. Grade III/IV leukopenia was greater in the regional HT arm (77.6%, vs 63%, p = 0.005). Hyperthermia-related AEs included pain, bolus pressure, and skin burn. In 2018, a long-term analysis of the same study was published.[15] After a median follow-up of 11.3 years, the RHT arm experienced a significantly improved local PFS (HR: 0.65; CI: 0.49–0.86, p = 0.002). Combination treatment resulted in significantly prolonged survival rates compared with the control (HR: 0.73, 95% CI: 0.54–0.98, p = 0.04). This trial produced one additional publication with a sub-group analysis of patients with abdominal or retroperitoneal high-risk STS.[14] The regional HT plus chemotherapy arm had improved five-year PFS (56% vs 45%, p = 0.044) and DFS (34% vs 27%, p = 0.040), but no difference in OS (57% vs 55%, p = 0.82).

Three controlled observational studies were identified; one used a Bone and Soft Tissue Tumor (BSTT) registry for comparison purposes,[56] and the others compared results with RT or CRT alone.[59,60] The BSTT registry comparison study reported that patients who received LRHT during chemotherapy (post-radiotherapy) did not experience a significant five-year OS benefit (78.3% vs 81.2%, p = 0.33). In the LRHT arm, the local-control rate at five years was significantly better (97.7% vs 85.1%, p = 0.017), and negative surgical margins were significantly higher (p < 0.0001). The other two controlled studies[59,60] both reported no significant benefit from LRHT, including local control (p = 0.39), DFS (p = 0.69), and response (p = 0.67). One of them[59] reported that cancer-specific mortality was significantly better compared with the control (p = 0.03), while the other[60] showed no significant benefit for two-year OS, local-control survival, or distant metastasis-free survival.

Two uncontrolled observational studies were identified. One included 64 participants with recurrent or residual STS who received LRHT with CRT.[57] Five-year survival was 86.4% (± 7.3%) and the local control rate was 86.7% (± 7.1%). The other study included 110 participants with locally advanced high-risk STS receiving combined chemotherapy and LRHT.[58] Disease control occurred in 59% of non-metastatic cases and 47% in those with metastases, with a median OS of 26 and 12 months, respectively.

Seven single-arm trials evaluated LRHT in combination with various treatments. Two of them applied LRHT with chemotherapy alone, with one[61] delivering LRHT in patients with high-grade STS on days 1 and 4 of neoadjuvant chemotherapy. After four cycles, mean tumour volume reduction was 49% (5% to 91%, SD: 27%). The other trial included patients with doxorubicin/ifosfamide-refractory STS receiving chemotherapy, seven of whom received LRHT.[62] Two of the seven patients experienced a PR.

Five single-arm trials explored LRHT specifically added to standard peri-operative care.[63-67] In one, 13 patients received LRHT and radiation, with five participants receiving pre-operative chemotherapy and seven post-operative chemotherapy.[65] Limb

salvation was possible for 12 of 13 patients; there was no local recurrence; the five-year survival was 40.4%, and DFS was 30.1%. Mean tumour volume reduction was 68.2%, with no participants experiencing CR, seven PR, three no change, and three progressing. Another study (n = 58) explored the use of combined LRHT with chemotherapy in both the neoadjuvant and post-treatment phase.[66] The overall OBJR rate (based on 40 evaluable patients) was 13%. Radiological response was 33%, and of the 30 who underwent treatment, six experienced pathological CR (23%). Median time to local relapse or progression was 21 months, with a median five-year OS of 31 months. One publication combined data from two phase II trials, exploring the use of neoadjuvant CRT and LRHT, surgery, and adjuvant CRT (without LRHT).[64] The OBJR rate (evaluable in 39 participants) was 21% with a median OS of 105 months. Five-year OS was 57%, with a five-year local recurrence-free survival of 48%. A similar single-arm phase II trial applied LRHT pre-operatively alongside chemotherapy, followed by post-operative radiation when indicated. Responders received additional chemotherapy and LRHT after surgery. The OBJR rate was 17%, median survival was 52 months, and five-year OS was 49%. The combination of pre-operative chemotherapy and LRHT, with radiation applied post-operatively, was further explored in another single-arm trial (n = 59).[63] The OBJR rate was 17%, with one CR and eight PR. Out of the total group, 49 were eligible for surgery. The overall five-year rate of local relapse-free survival was 40% and the median survival was 52 months, with a five-year OS of 49%. One final study delivered LRHT in combination with neoadjuvant chemotherapy for patients with poorly resected, non-metastatic, STS.[67] The overall OBJR rate was 16%, of which all were partial. Median time to local relapse or progression was 21 months, median OS was 33 months, and the four-year OS rate was 40%.

General Soft Tissue Tumours

Two studies included patients with malignancies other than STS. One single-arm trial included a mix of different deep-seated, advanced sarcomas.[68] In addition to standard supportive care, participants received LRHT with chemotherapy. Based on 61 evaluable participants, overall OBJR was 34%, and 13 patients who were initially deemed to have unresectable disease were eligible for surgery. One observational study included patients with unresectable and/or recurrent mixed soft-tissue tumours, applying a combination of LRHT and radiation.[69] This produced a CR in 42% of tumours treated, with a five-year survival of 32%.

Other Cancer Types

The original literature review identified and described studies of LRHT for cancers of the bladder,[12,70-72] brain,[73-75] colon/rectum[76-92] and anus,[93] hepatobiliary,[94-97] lymphatic system (Hodgkin's lymphoma)[98], lung[21,22,27,99-109], skin (melanoma),[17,18,110-113] ovary,[114-120] pancreas,[9,121-129] prostate,[130-133] and vagina and vulva,[134] as well as studies including mixed cancer types. Detailed descriptions for each cancer can be found in the complete monograph.

Quality of Life (QoL) and Symptom Management

Relatively few studies included QoL endpoints,[27,29,38,50,79,90,91,105,106,115] and many were single-arm trials, making interpretation challenging. Two RCTs reported improvements in QoL; in patients with cervical cancer, fatigue, cognitive, and social functioning improved,[29] and in patients with non-small cell lung cancer (NSCLC), physical, emotional, and global QoL as well as symptoms of pain, fatigue, nausea, shortness of breath, and appetite loss significantly improved.[27] Three single-arm trials[38,79,90] and one chart review[106] reported reductions in pain. However, one retrospective study reported increases.[105] Two studies found no change in QoL.[91,115] Ultimately, based on limited data, QoL support is not a primary or recommended indication for use.

Safety

Adverse Events

Locoregional HT is generally safe and well tolerated,[135,136] especially with contemporary technology.[5] Toxicity in patients receiving chemo- and/or RT, with or without LRHT, is typically comparable.[135] Technology advances, treatment planning, and guideline availibility[137-140] have improved tolerability.[5] Thus, safety and toxicity concerns from older studies should be interpreted judiciously. The following AEs have been attributed to HT in recent years (post-2000): discomfort during treatment,[60,63,78,79] mild pain,[25,62,123,135] local erythema,[32,62,66,67] skin/superficial burn (mild-moderate; grade 1–2),[29,13,56,135] and, less commonly, subcutaneous thermal injury/adipose burns.[9,133,30]

There are several cardiorespiratory effects specifically observed with deep regional HT that may affect safety. Changes include slightly increased core temperature (38.2±1.4 vs 36.6±0.8, $p < 0.001$), tachycardia (104±15 vs 85±16 bpm, $p < 0.05$), decreased respiratory rate (23±3 vs 21±3/min, $p < 0.05$), transient orthostatic hypotension after completion of treatment, reduced oxygen saturation (95±2% vs. 97±1%, $p < 0.05$), and fluid loss through sweating when compared with baseline.[141]

Interactions

Other Cancer Therapies: Locoregional HT is considered a chemosensitizer and radiosensitizer[5] and is regularly used with chemotherapy and radiation as reviewed above. There is insufficient evidence for the combined use of HT with targeted therapies including monoclonal antibodies and small molecule inhibitors, or endocrine therapies.

Other Medications: Locoregional HT should be used cautiously with medications that can alter a patient's consciousness, pain perception, or ability to communicate.

Other Complementary and Alternative (CAM) Therapies: No reports of negative interactions for LRHT and other CAM treatments were found.

Cautions and Contraindications

Common contraindications include:[142,143]

- Patients with implanted/worn/carried medical devices, implants, or any foreign objects
- Inability to feel or respond to pain, including sedation, loss of consciousness, and severe neuropathy
- Systemic fever > 38°C[140]
- Severe pulmonary disease (Forced Expiratory Volume (FEV) < 50%)
- Cardiovascular high-risk patients
- Severe cerebrovascular disease
- Treatment delivered to areas of prior irradiation
- Known decreased circulation in heated area
- Patients prone to hemorrhage, presence of an open wound
- Patients with organ transplant
- Children (due to lack of evidence)

DISCUSSION

Locoregional HT for cancer care can be found in a few North American complementary health clinics, most often offered by naturopathic doctors. Despite the rich research landscape of HT, a comprehensive review of all cancer types was not identified. This review describes the cancers with the strongest evidence for benefit with adjunctive LRHT. There is some encouraging evidence for improvements in OBJR rates, and conceivably survival, for patients with certain cancer types, while in other areas the evidence is preliminary and/or too heterogeneous to form conclusions.

For patients with locally recurrent breast cancer receiving radiotherapy, the addition of HT likely improves CR rates and disease control based on results of a meta-analysis.[11] Less is known about the use and effects of LRHT for patients with different breast cancer presentations (e.g., metastatic disease). For cervical cancer, there is consistent and strong evidence that the addition of LRHT to radiation therapy and chemoradiation for patients with stage II–IVa disease is beneficial. Further studies are needed to determine the magnitude of effect and impact on unique subgroups of patients who may benefit. For patients with esophageal cancer, results are suggestive of benefit for response rate and survival outcomes when combined with neoadjuvant conventional care. Although results were consistent across studies, the quality of the RCTs was generally low. Locoregional HT is a promising treatment to improve survival in advanced gastric cancer and as a neoadjuvant treatment for operable gastric cancer. Combined with RT, HT may improve response rates in patients with locally advanced HNC based on controlled trials, and further research is warranted for combination with CRT. Evidence demonstrates a benefit for PFS and OS in patients with localized, high-risk STS treated with neoadjuvant and adjuvant LRHT with chemotherapy compared with chemotherapy alone. The evidence for the use of HT in other settings with sarcomas or other soft-tissue tumours is unclear.

Treatment methods including timing of LRHT in relation to conventional treatment, frequency, and duration are important clinical considerations. Quality assurance guidelines for HT state that chemotherapy is to be given just before or simultaneous to HT, and radiation be given ideally within one hour of HT (but up to four hours is acceptable).[138] This guideline is consistent with the methods used by almost all studies. The target tumour temperature ranges for LRHT are 39°C to 45°C, however 41°C to 43°C is considered optimal.[4,5] Based on RCTs (Table 2), LRHT is most commonly administered once or twice weekly for the duration of conventional treatment, with each session typically lasting 60 to 90 minutes.[140]

Multiple theories of mechanism of action exist for HT, including mitigating hypoxia and inflammation via perfusion and oxygenation changes,[3] damaging tumour vasculature,[3] and denaturing structural proteins.[144] Synergistic effects with chemotherapy include increasing cell membrane permeability and drug uptake by malignant cells[3] and enhancing chemotherapeutic cytotoxicity.[145] When combined with radiation, HT may offset hypoxia-associated radioresistance,[136] suppress cancerous DNA damage repair,[136] and augment advantageous proapoptotic effects[3] and reactive oxygen species.[136]

The studies included in this review have several limitations. First, most of the studies were single-arm or observational. These studies have a greater risk of bias as they lack controls and blinding, making it difficult to determine the effect of the LRHT compared with the other treatments. Many of the studies had small samples sizes, in some cases fewer than 10 people. Again, this weakens the strength of the conclusions and often leaves the studies underpowered to detect clinical outcome changes. Technology has significantly changed in the past two decades, with studies published prior to 2000 often reporting higher AE rates and not always having proper treatment planning or the ability to achieve target temperature and duration.[4,5] In addition, changes to conventional care within contemporary settings may not reflect the standards of care provided in some older trials, rendering them not comparable/relevant.

There are several limitations to this review. First, a rigorous evaluation and quality assessment including risk of bias using a validated tool was not performed. Although some qualitative description of trial quality was provided, without a standardized approach, some poorer-quality studies may have been overrepresented and, alternatively, higher-quality studies not given sufficient attention. Second, the quality and types of studies included have a high degree of population and co-treatment heterogeneity, making interpretation and comparison of results challenging. Lastly, due to the sheer number of studies included, a full description of the trials and outcomes could not be practically provided. In addition, the heterogeneity and scope of the work performed did not allow for meta-analysis.

Moving forward, high-quality RCTs are necessary for most cancer types to assess the efficacy and magnitude of the effect of LRHT and create changes to practice. Future studies should be sufficiently powered with a large enough sample size to enable the clinical effect to be observed, low risk of bias with proper randomization including allocation concealment, and the appropriate population type, as well as proper quality assurance of

treatment application. Additionally, studies using LRHT alongside newer cancer treatments, including immunotherapy, monoclonal antibodies, and tyrosine kinase inhibitors, are needed as these therapies are being increasingly used in oncology.[146,147]

Data Sharing Statement

Additional information, including access to the complete monograph, is available upon request. Please contact Dugald Seely, ND, MSc at dseely@thechi.ca.

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