JAMEA

JOURNAL OF ADVANCED MECHANICAL ENGINEERING APPLICATIONS
e-ISSN: 2716-6201

Vol. 7 No. 1 (2026) 105-114
https://publisher.uthm.edu.my/ojs/index.php/jamea

Analysis of Thermal Synergy and Thermal Overlapping in Multifocal Breast Tumor Hyperthermia Therapy

Nur Amani Hanis Roseman[1], Ishkrizat Taib[1]*

[1] *Department of Mechanical Engineering, Faculty of Mechanical Engineering and Manufacturing, Universiti Tun Hussein Onn Malaysia, Batu Pahat, Johor, 86400, MALAYSIA*

*Corresponding Author: iszat@uthm.edu.my
DOI: https://doi.org/10.30880/jamea.2026.07.01.011

Article Info

Received: 27 February 2026
Accepted: 21 May 2026
Available online: 30 June 2026

Keywords

Hyperthermia, breast tumor clustering, computational fluid dynamics (CFD), thermal synergy, inter-tumor interaction, temperature uniformity, thermal overlap

Abstract

Hyperthermia is a promising complementary treatment which improves the therapeutic efficacy of conventional cancer therapies by utilizing controlled elevation of tumor temperature. Although numerous studies have investigated temperature distribution in individual breast tumors, the behavior of thermal interaction between multiple tumor regions remains inadequately quantified. This study presents a secondary analysis of previously obtained computational fluid dynamics (CFD) simulation data to assess thermal interaction in single and triple clustered breast tumor configurations exposed to hyperthermia treatment. Temperature profiles were extracted and analyzed for tumor diameters of 2 and 4 cm under 40°C, 45°C and 50°C heating conditions. Three quantitative metrics were evaluated including thermal overlap, inter-tumor thermal variation (ΔT) and thermal synergy index (TSI). The findings demonstrate that clustered tumors constantly exhibited bigger thermally affected regions in comparison to equivalent single tumor configurations. This may indicate stronger spatial interaction of thermal regions. Nevertheless, clustering also increased temperature heterogeneity with ΔT values rising from 4.72°C to 15.26°C and 7.60°C to 16.43°C as heating condition elevated from 40°C to 50°C in 2 and 4 cm tumors' cluster respectively. Thermal synergy analysis displayed a temperature dependent behavior as TSI value increased from 0.991 at 40°C to 1.018 for 2 cm tumors and consistent positive synergy for 4 cm tumor reaching a maximum TSI value of 1.021 at 50°C. Findings observed in this study reveal that clustering tumor increase conductive thermal interaction as well as promotes synergy heat buildup at high temperatures but accompanied by a reduction in thermal uniformity. Therefore, this study provides a quantitative framework to evaluate thermal interaction involving multifocal breast tumor. It also offers supplementary insight into the influence of heating intensity and tumor size on hyperthermia treatment performance.

1. Introduction

Breast cancer has remains as one of the most prevalent malignancies affecting females worldwide and it continues to contribute significantly to cancer related mortality cases. Fig. 1 illustrates the temporal trends in cancer

mortality rates in the Malaysia from year 2000 to 2022 for various cancer types. Breast cancer remained the top three leading causes of cancer-related mortality throughout the period, its mortality rate showed a noticeable reduction in 2019 and continued increasing afterward [1], [2]. This reduction may reflect the changes in reporting patterns as well as increased research attention on cancer overtime. The advances in early detection techniques and the development of more effective treatment strategies also play some role.

Among the available treatment approaches, hyperthermia therapy has been established as a promising adjuvant treatment modality. It gained increasing attention due to its capability to elevate target tumor tissues to supraphysiological temperatures typically within range of approximately 40–45°C for a sustained period [3]. This thermal dose employs direct cytotoxic effects on cancer cells while simultaneously enhancing the efficacy of conventional radiotherapy and chemotherapy by increasing blood perfusion, improved oxygenation, promote tumor cell sensitivity and inhibit the DNA repair pathways [4], [5]. The therapeutic benefit is critically reliant on attaining homogeneous temperature elevation across the entire tumor volume [6]. Insufficient heating may reduce treatment effectiveness whereas excessive heating can cause damage to the surrounding healthy breast tissues [7]. It is a challenge in achieving controlled and localized temperature elevation during hyperthermia and that becomes considerably more complex when multiple tumors are present.

In multifocal or clustered breast tumors, thermal behavior becomes more complex cause by the interaction between neighboring tumors heating zones. These may generate overlapping thermal fields that can alter local temperature distribution, the heat penetration as well as temperature uniformity. In certain cases, the phenomenon of thermal overlap may be therapeutically advantageous by creating thermal synergy but poses substantial risk of unintended thermal injury to normal tissues [8], [9]. Understanding thermal characteristics of closely spaced tumors and their heat interaction may improve treatment safety regarding thermal merging during hyperthermia therapy.

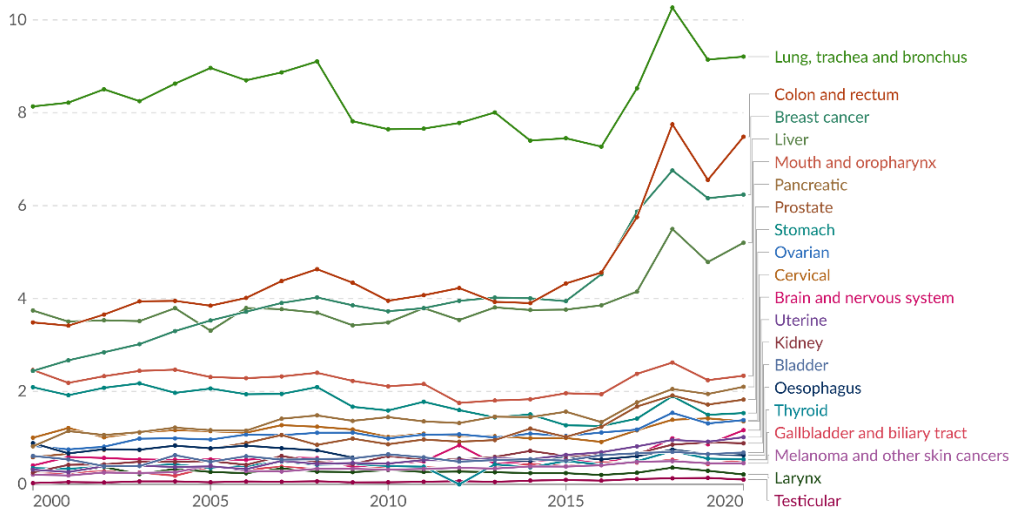

Fig. 1 *Trends in cancer death rates by cancer type in the Malaysia between 2000 to 2022 (per 100,000 population)* [2]

Previous studies on breast hyperthermia primarily focused on isolated tumor behavior and general temperature visualization using computational and experimental approaches [10] – [13]. Although such investigation yielded valuable insights into tumor size effects, heat propagation, perfusion effects and thermal performance, it provides limited attention about thermal overlap mechanism and thermal interaction behavior in clustered tumor configurations. Quantitative evaluation of thermal merging characteristics, temperature uniformity and overlap behavior remains insufficiently discussed.

Therefore, this study aims to investigate the thermal interaction, overlapping heat distribution in clustered breast tumors during hyperthermia treatment using previously obtained computational temperature distributions [14]. The present study emphases the analysis of thermal overlap percentage, the thermal plateau formation, inter-tumor temperature variation as well as thermal synergy behavior through interpretation of temperature contour distributions and front-to-back temperature profile data. The findings of this study are anticipated to offer additional understanding into thermal field interaction mechanisms and improved thermal management in breast hyperthermia applications which thereby provide guidance for treatment planning in patients presenting with multifocal breast disease.

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2. Methodology

2.1 Numerical Model and Temperature Data Source

The temperature distribution data analyzed in the present study were obtained from previously completed computational fluid dynamics (CFD) simulations of breast hyperthermia treatment [14]. The numerical model used consists of breast tissue containing single and triple clustered tumor configurations subjected to external hyperthermia heating conditions as shown in Fig. 2. The tumor diameters of 2 cm and 4 cm were investigated under heating temperatures of 40°C, 45°C, and 50°C. The simulations were performed using bioheat transfer module in ANSYS Fluent based on Pennes' bioheat equation to model heat transfer and temperature propagation within the breast tissue domain. The Pennes' bioheat equation has been a foundational model in bioheat transfer research since its introduction in 1948 [6]. The present work focuses on quantitative interpretation of the existing temperature distributions [14] to evaluate thermal overlap behavior and heat interaction characteristics.

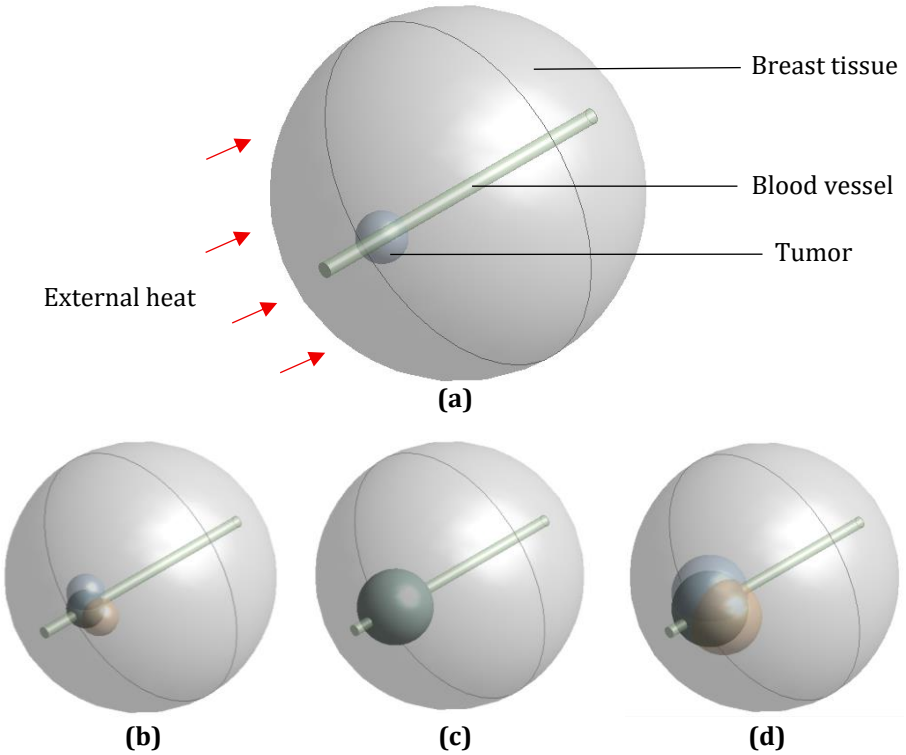

Fig. 2 *Computational breast tumor model used in previous simulation study; (a) Single 2 cm tumor; (b) Triple clustered 2 cm tumors; (c) Single 4 cm tumor; and (d) Triple clustered 4 cm tumors* [14]

2.2 Thermal Overlap Analysis

The thermal overlap percentage was applied to quantify the spatial extent of continuous therapeutic heating within the tumor interaction region. The therapeutic overlap length ($L_{therapeutic}$) was defined as the continuous distance along the temperature profile in which the local temperature remained above 42°C of therapeutic threshold. It is known that temperatures above 42°C may induce cytotoxic effects in tumor cells [15] – [17]. The thermal interaction length ($L_{interaction}$) was expressed as the total spatial region affected by tumor-induced heat propagation which extends from the point where temperature first increased above the baseline physiological levels to where it returned to baseline.

The overlap percentage was then calculated using the following formula:

$$\text{Overlap } \% = \frac{L_{therapeutic}}{L_{interaction}} \times 100 \tag{1}$$

Higher overlap percentages indicate a stronger merging of thermal fields as well as a broader continuous therapeutic coverage within the triple clustered tumor configuration.

2.3 Inter-tumor Temperature Variation

The temperature uniformity within the clustered tumor configurations was calculated through inter-tumor temperature variation analysis. The thermal plateau was identified to show continuous stable regions of relatively stable temperatures distributions by overlapping thermal fields. Regions exhibiting smaller inter-tumor temperatures differences were taken as having stronger thermal interaction and a more uniform heat propagation behavior. This was quantified by the maximum and minimum temperatures difference within cluster tumor using equation:

$$\Delta T = T_{max} - T_{min} \tag{2}$$

Where the T_{max} is defined as the maximum temperature within tumor heating region and T_{min} represents the lowest temperature within continuous thermal interaction region. A low temperature variation, ΔT, indicates an improved thermal uniformity and a stronger heat distribution continuity between tumor cluster. Fig. 3 illustrates temperature profile for a triple tumor cluster. The red circle marks indicate tumor peak, T_{max} and T_{min}. The continuous thermal plateau region generated by overlapping thermal fields was presented in the shaded area. The calculated differences were used to further evaluate the degree of thermal merging within clustered tumors during hyperthermia treatment.

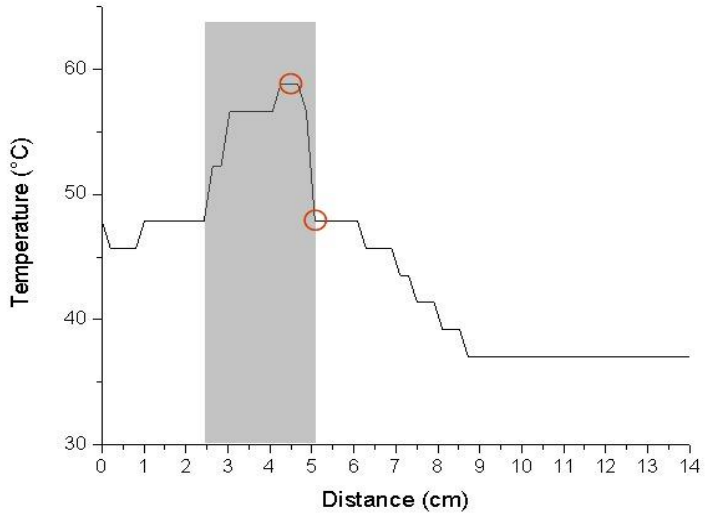

Fig. 3 *Temperature profile graph indicating T_{max}, T_{min} (red circle) and the thermal plateau region (grey band) for clustered tumors configuration* [14]

2.4 Thermal Synergy Analysis

Thermal synergy index (TSI) was calculated to analyze thermal synergy between clustered tumor configurations. It is used to compare heating performance of clustered tumors to single isolated tumor models. The TSI was calculated using:

$$\text{TSI} = \frac{T_{cluster}}{T_{single}} \tag{3}$$

$T_{cluster}$ denotes the peak temperature among the three clustered tumor configurations whereas the T_{single} represents peak temperature obtained from single isolated tumors under identical heating conditions. A greater TSI value (TSI > 1) indicates positive synergy in clustered tumors and thus illustrates enhanced thermal behavior. TSI value equal to 1 (TSI = 1) implies no interaction. The TSI was calculated for each hyperthermia temperature (40, 45 and 50°C).

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3. Results and Discussion

3.1 Thermal Overlap Behavior

The thermal overlap behavior of triple clustered breast tumor configurations was evaluated to calculate the spatial interaction between tumor heating region during hyperthermia therapy. A therapeutic overlap region was defined when the continuous region exceeds temperature threshold of 42°C. Fig. 4 shows representative temperature contour distributions displaying the thermal interaction. This demonstrated that thermal overlap rises progressively with external heating temperature for all triple clustered tumor configurations indicating strong thermal interaction among adjacent tumor.

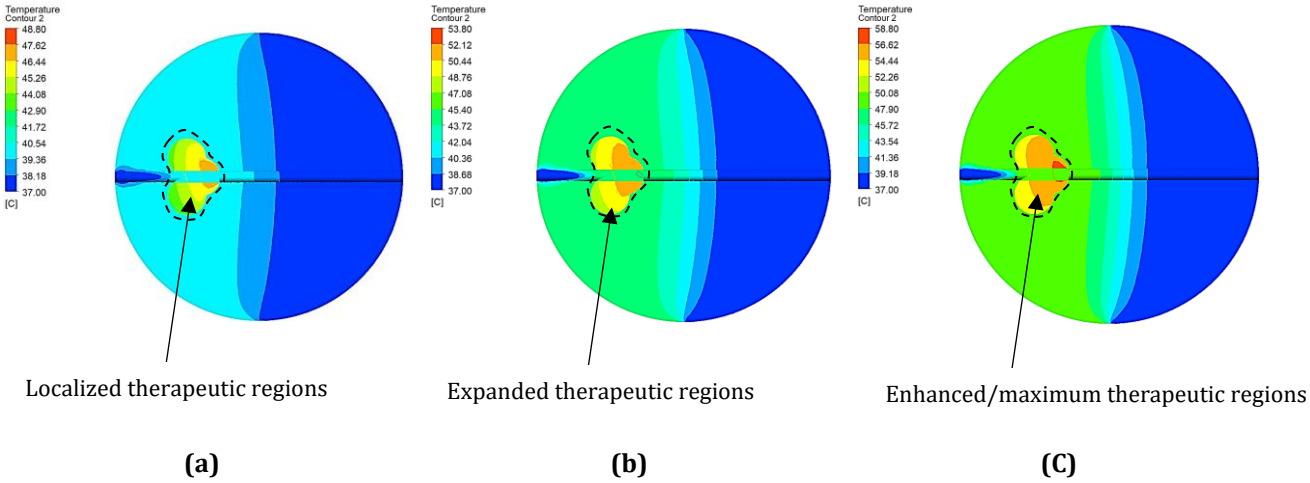

Fig. 4 *Temperature distribution in 2 cm triple clustered tumor; (a) 40°C; (b) 45°C; and (c) 50°C (dashed line represents the 42°C therapeutic threshold within tumors)* [14]

In Fig. 5, the overlap percentage increase in clustered 2 cm tumors from 90.9% at 40°C to 93.3% at 50°C external hyperthermia heating. Similarly, clustered 4 cm tumors exhibited an increase from 86.8% at 40°C to 95.0% at 50°C. These findings show that increasing heat intensity of hyperthermia therapy enhances the conductive heat propagation within the breast tissue domain. This resulted in a much broader therapeutic coverage as well as stronger thermal merging between tumors.

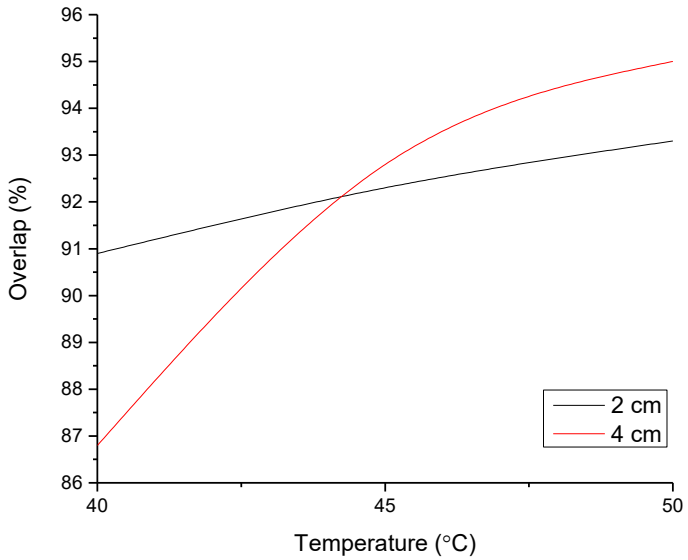

Fig. 5 *Thermal overlap percentage for clustered tumor configurations*

These findings are consistent with previous computational studies which reported that spatial thermal interaction becomes significantly dominant under higher heating conditions [18], [19]. Increasing thermal loading

improves heat propagation and promote a wider coverage of therapeutic temperature in hyperthermia system [20]. The overlap analysis demonstrates that the configurations of clustered tumor can considerably enhance therapeutic heat coverage but also increase the risk of excessive heating within merged thermal regions. Therefore, the optimization of hyperthermia heat intensity and tumor targeting strategies remains a crucial goal for an effective therapy.

3.2 Inter-Tumor Temperature Variation and Thermal Uniformity

The quantification of tumor temperature variation (ΔT) provides an indication of temperature uniformity. A small value of ΔT correspond to a more homogeneous heating whereas larger values show stronger thermal gradients. The calculated ΔT values for both 2 cm and 4 cm clustered tumor configuration are tabulated in Table 1. Each tumor sizes showed a progressive increase in ΔT with heating temperatures. The temperature variation in 2 cm cluster increased from 4.72°C at 40°C to 10.08°C at 45°C and it further increase to 15.26°C at 50°C. A similar trend was seen for 4 cm cluster as the ΔT value increased from 7.60°C to 12.36°C and 16.43°C at the rises of heating temperature respectively.

Table 1 *Inter-tumor thermal variation (ΔT) in clustered tumor configuration*

Tumor Size (cm)	Heating Temperature (°C)	ΔT (°C)
2	40	4.72
2	45	10.08
2	50	15.26
4	40	7.60
4	45	12.36
4	50	16.43

These results demonstrate that higher heating temperatures will produce greater temperature non-uniformity within the tumor cluster. Although elevated hyperthermia heating enhances the thermal penetration and therapeutic coverage, it concurrently produces larger spatial temperature gradients. Findings suggest that the increase in thermal energy become increasingly intense around areas of overlapping heat accumulation. Thus, localised hotspots were generated while nearby regions remain reasonably cooler.

Fig. 6 showed the comparison between tumor sizes. It further reveals that 4 cm cluster consistently displayed higher thermal variation values than 2 cm cluster under similar heating conditions. This behavior may be due to the large, heated volume of 4 cm tumors which promotes greater conductive heat propagation as well as a much stronger temperature gradient across the tumor cluster.

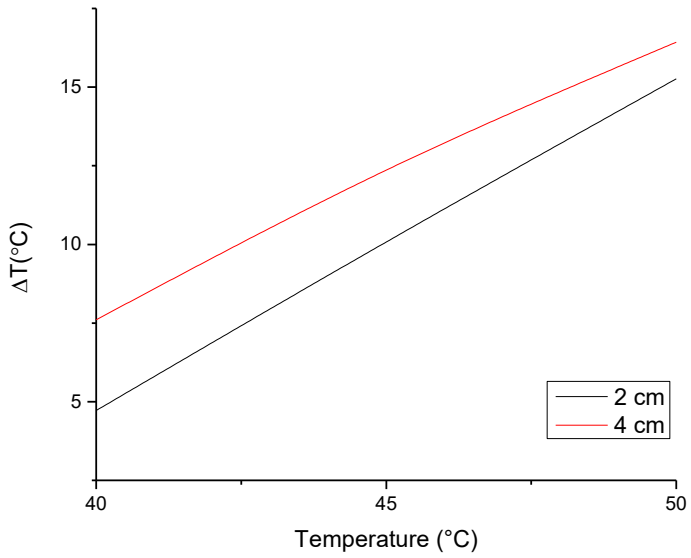

Fig. 6 *Variation of ΔT with heating temperature for 2 cm and 4 cm triple clustered tumors*

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The observed rise in temperature heterogeneity with hyperthermia heating intensity is consistent with previous studies which stated that local heat accumulation and conductive contacts with adjacent heated regions may generates substantial temperatures non-uniformities within biological tissues [21]. Previous study of computational hyperthermia investigations based on the Pennes bioheat equation has also discussed such behavior where conductive heat transfer dominates local temperature distribution when the thermal sources are situated in proximity [13, 14, 21]. Overall, the findings determine that clustered tumor exhibit strong thermal gradients progressively as hyperthermia heating temperature increases. High thermal interaction improves heat coverage but excessive ΔT may lead to reduction of treatment uniformity and raise the risk of local overheating.

3.3 Thermal Synergy Behavior

The thermal synergy index calculated as the ratio of maximum temperature achieved within the clustered tumor to maximum temperature obtained in the corresponding single tumor models. Table 2 presented the calculated TSI values. The TSI values for 2 cm tumors were 0.991, 0.983 and 1.018 at hyperthermia heating temperatures of 40°C, 45°C and 50°C respectively. The value below 1 indicates that the tumor clustering did not provide thermal amplification but instead generates slight reduction in peak temperature. The emergence of positive thermal synergy was only seen at 50°C as the TSI value exceeds unity.

Table 2 *TSI for clustered tumor configurations*

Tumor Size (cm)	Temperature (°C)	T_{max} Triple (°C)	T_{max} Single (°C)	TSI
2	40	47.62	48.03	0.991
2	45	52.12	53.03	0.983
2	50	58.80	57.74	1.018
4	40	49.66	49.25	1.008
4	45	54.66	54.25	1.008
4	50	60.47	59.24	1.021

In comparison, a different behavior was observed for 4 cm tumor cluster. The TSI values remained above unity for all heating conditions. Although scale of enhancement was relatively small, the findings suggest larger tumor cluster steadily promote constructive thermal interaction between adjacent thermal areas. The rise in TSI with heating proposes that thermal synergy is temperature dependent as illustrated in Fig. 7. Higher heat intensity led to stronger overlap in thermal fields thereby causing more heat accumulation and higher peak temperature. Furthermore, positive synergy, highest thermal overlap and largest thermal variation values were all observed at 50°C of hyperthermia heating. This shows that thermal synergy and thermal disparity are closely associated phenomena. Robust heat accumulation enhances thermal interaction but also simultaneously encourages bigger temperature gradients within tumor region.

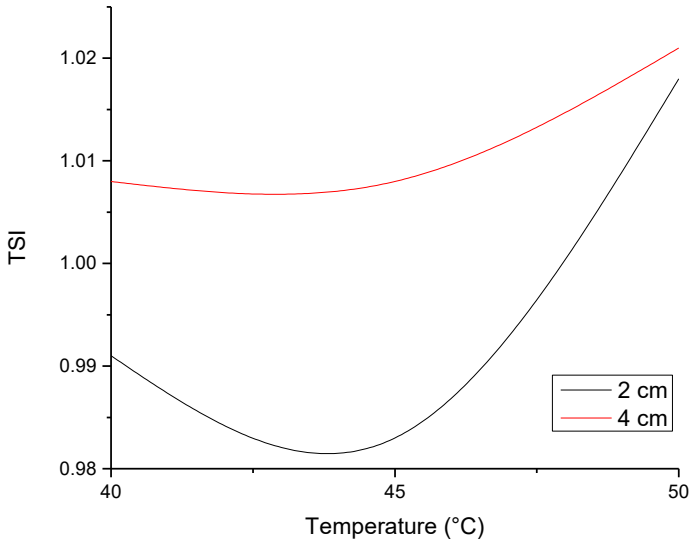

Fig. 7 *TSI as a function of heating temperature*

In clinical practice, exploiting thermal synergy should not be considered as the sole objective because unnecessary heat accumulation can produce larger temperature gradients. An optimal heating condition which provides adequate overlap to ensure complete tumor coverage while maintaining temperature variation within acceptable range needs to be identified. This balance can be achieved by adjusting heating temperature, the duration of treatment or applicator placement based on the tumor size and clustering pattern that cater to each specific patient.

3.4 Overall Thermal Interaction Behavior in Clustered Tumors

The combined analysis of these thermal performance metrics including thermal overlap, inter-tumor temperature variation and thermal synergy provides a much more comprehensive characterization of thermal interaction mechanism within clustered breast tumor during hyperthermia treatment. Thermal overlap analysis displayed that elevated heating temperature increases spatial merging of therapeutic area which indicates enhance conductive heat propagation between adjacent tumors. Besides, temperature variation raised significantly with temperature yet reflects deterioration in thermal uniformity as well as steeper gradients in clustered tumor. In addition, thermal synergy analysis further demonstrated that clustering can improved peak temperature generation with sufficient heating conditions as evidenced by the transition toward mild positive synergy at higher temperatures. This suggests that conductive heat buildup becomes prominent once enough thermal energy is supplied.

Collectively, increased spatial overlapping regions, elevated temperature gradients within cluster and constructive enhancement of peak temperature are interconnected processes which develop thermal interaction. However, the same mechanism may promote the likelihood of uneven temperature and overheating. Thus, optimizing hyperthermia treatment for clustered breast tumors should balance the aids of enhanced thermal interaction against the risk related to unwarranted thermal heterogeneity. The findings of this study deliver quantitative evidence in which tumor size as well as heating intensity plays as key governing parameter influencing thermal interaction in clustered tumor configurations.

4. Conclusion

This study evaluated thermal interaction in single and triple clustered breast tumor configurations by analyzing CFD derived temperature profiles obtained under hyperthermia heating conditions of 40°C, 45°C and 50°C for tumor diameter of 2 and 4 cm. The results demonstrated that cluster tumors produced larger thermally affected regions than single tumors. Thermal overlap increased with high heat intensity for both tumor sizes which reflects greater merging of therapeutic regions. Moreover, temperature variation rises also with heating temperature. This heat accumulation may lead to decrease in thermal uniformity. Furthermore, thermal synergy was revealed to be a temperature dependent response which varied with tumor size. The transition exhibited by 2 cm clustered tumor configuration from slight thermal suppression (TSI<1) at low heat setting to positive thermal energy (TSI>1) at 50°C whereas 4 cm clustered configuration showed positive synergy across all investigated heating conditions. This behavior indicates that tumor size influences the effectiveness of thermal coupling as well as heat accumulation within clustered environments. Overall, the findings in this study suggest that tumor clustering may improve thermal interaction and coverage but could result in increased uneven temperature at high hyperthermia heating conditions. The proposed thermal performance metrics offer a useful framework in interpreting temperature distribution and assist as the base for treatment planning of multifocal breast tumor using hyperthermia. Future work should incorporate thermal dose metrics and experimental validation to further explore the association of tumor geometry, tissue heterogeneity and thermal interaction behavior throughout hyperthermia treatment.

Acknowledgement

This research was supported by the Malaysian Ministry of Higher Education (MOHE) through the Fundamental Research Grant Scheme (FRGS) (FRGS/1/2022/TK10/UTHM/03/5).

Conflict of Interest

Authors declare that there is no conflict of interest regarding the publication of the paper.

Author Contribution

The authors confirm contribution to the paper as follows: ***study conception and design:*** *Roseman NAH, Taib I;* ***data collection:*** *Roseman NAH;* ***analysis and interpretation of results:*** *Roseman NAH;* ***draft manuscript preparation:*** *Roseman NAH. All authors reviewed the results and approved the final version of the manuscript.*

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