This review discusses available clinical and experimental data and the underlying mechanisms involved in trimodality treatment consisting of hyperthermia, cisplatin and radiotherapy. The results of phase I/II clinical trials show that trimodality treatment is effective and feasible in various cancer types and sites with tolerable toxicity. Based on these results phase III trials have been launched to investigate whether significant differences in treatment outcome exist between trimodality and standard treatment. In view of the clinical interest it is surprising to find so few preclinical studies on trimodality treatment. Although little information is available on the doses of the modalities and the treatment sequence resulting in the largest degree of synergistic interaction, the results from in vivo and in vitro preclinical studies support the use of trimodality treatment for cancer patients. Animal studies show an improvement in treatment outcome after trimodality treatment compared with mono- and bimodality treatment. Studies in different human tumor cell lines show that a synergistic interaction can be obtained between hyperthermia, cisplatin and radiation and that this interaction is more likely to occur in cell lines which are more sensitive to cisplatin.