The heating of diseased tissue as a therapeutic measure has gained increased clinical attention, mostly due to its target-specificity that minimizes side effects. However, to ensure a successful therapy, heating has to be homogeneous and highly localized, as well as, within a certain temperature range. Therefore, precise control over thermal treatments is a clinical prerequisite to minimize treatment and safety margins. Although this requirement is mentioned frequently, past research has focused predominantly on improving thermometry resolution and heating efficiency through tedious material optimization. Here, current clinical applications of thermal therapy with their challenges are first highlighted, especially with respect to treatment control and margins. Thereafter, it is quantitatively shown that clinically available thermometry fulfills the requirements and future research should focus on achieving better temperature control instead. With nanotechnology, novel strategies based on self-limiting nanoparticle systems and particle-based thermometers with active feed-back control have also become available and are discussed. All of these approaches are systematically compared and analyzed with respect to their clinical applicability. The extent to which control over thermal therapy is necessary is also discussed alongside a presentation of the existing methods which fulfill the set requirements for clinical success and what issues remain to be tackled by research in the near future.

1. Thermal Therapy in Clinics

Surgical excision and radiotherapy are among the most common treatments for solid organ neoplasms (i.e., tumors). As the exact microscopic boundaries of diseased tissue cannot be determined precisely or are rather diffuse, safety margins are added to the treatment volume to ensure complete tumor control. The safety margins vary depending on tumor type and treatment modality as a result of functional organ volume necessity or sensitivity of adjacent tissue. Table 1 (and Table S1, Supporting Information) shows clinically used safety margins for both surgical removal and radiotherapy of various tumor types. For radiotherapy, in addition to safety margins, treatment margins are also reported, which are a result of the diffuse boundaries of the tissue volume absorbing the sufficient radiation dose.

These margins are crucial for tumors in the vicinity of important structures. For example, in treatment of head and neck malignancies, in particular laryngeal or hypopharyngeal carcinomas (Figure 1a), collateral damage to the carotid artery can lead to rapid exsanguination, damage to the esophagus to an inability to eat or drink, or involvement of the laryngeal airway to respiratory compromise. Similarly, small and/or diffuse cancer can pose treatment dilemmas, in particular for surgical resection, where extensive removal of tissue can lead to near-total organ dysfunction. Examples are multiple lung (Figure 1b) or liver neoplastic deposits. Although radiotherapy can overcome some of the access limitations of surgery, the problems described above apply also. Sufficient observation and precise control of the...
Table 1. Margins of surgery and radiotherapy for representative cancer types. (SCC: squamous cell carcinoma).

| Cancer            | Surgical safety margin [mm] | Radiotherapy safety margin [mm] | Radiotherapy safety + treatment margin [mm] |
|-------------------|-----------------------------|-------------------------------|------------------------------------------|
| Lung              | 20^{(1)}                   | 5–8^{(2)}                    | 15–23^{(2)}                               |
| Liver             | 10^{(3)}                   | 5^{(4)}                      | 10^{(4)}                                  |
| Prostate          | N/A                         | >3^{(5)}                     | 11–16^{(5)}                               |
| Head and neck SCC (mucosal) | 5^{(6)}                  | 5^{(7)}                      | 10^{(7)}                                  |
| Breast            | 2^{(8)}                     | 10–15^{(9)}                  | 20–25^{(9)}                               |

radiation dose to the target and collateral tissue are especially limiting factors.

Thermal therapy has been suggested as a more selective and precise therapeutic alternative. It describes the treatment of diseased tissue (i.e., tumors) by heating. Therapeutic temperature levels vary between applications and, as a result, also treatment times range from a few seconds to several minutes. Extended heating at lower temperatures is classified as hyperthermia treatment, while short exposure to higher temperatures is specified as thermal ablation. In contrast to the more established surgery and radiotherapy, no clearly defined safety or treatment margins are available for thermal therapies, making a direct comparison difficult. Therefore, in the following the benefits and limitations of thermal therapy are evaluated in order to benchmark it against the other treatments.

Currently, two main heating techniques are predominantly used in clinics: radiofrequency ablation (RFA) and microwave thermosphere ablation (MTA). While the former has been used since the early 2000s, the latter was approved for use by the FDA in 2014.\(^{10}\) The RFA uses high-frequency alternating current to generate thermal energy, leading to a spherical volume of tissue being heated at the applicator tip. This results in ablation zones of up to 5 cm and can either be temperature- or impedance-regulated.\(^{11}\) The RFA has some limitations, with the process taking up to 30 min to create an ablation zone of 5 cm. It has also been described as being susceptible to the heat-sink effect (i.e., cooling through blood-flow), especially when close to large vessels.\(^{12}\) The MTA on the other hand uses electromagnetic waves to generate heat. This results in more homogenous tissue ablation and less susceptibility to heat-sinking.\(^{13}\)

Currently, thermal ablation methods can achieve a local tumor control rate between 60% and 96%, depending on neoplasm type and location.\(^{14}\) Factors associated with local tumor recurrence included large tumor size (>3 cm), ablation margin some smaller than 0.5 cm, and proximity to large vessels. This has led\(^{11}\) to advocating for larger, 1 cm ablation margins.

Thermoaulation treatments can either be delivered using open or laparoscopic surgical approaches, which rely on direct visualization, or percutaneous approaches. The latter is the least invasive and can be performed without general anesthesia. However, they rely on placement under image guidance, including ultrasound (US), computer tomography (CT), or magnetic resonance imaging (MRI).\(^{15}\) They also have a slightly higher risk for recurrence at the ablation site, when compared to other approaches.\(^{16}\) Laparoscopy, on the other hand, combines some of the advantages of percutaneous and open methods. It allows for minimally invasive access, while also utilizing image guidance, such as ultrasound, intra-operatively.\(^{17}\)

1.1. Lung Cancer

Lung cancer accounts for the highest number of cancer deaths worldwide.\(^{18}\) At present surgical resection remains the gold standard for early-stage lung malignancies. For patients with significant comorbidities, poor performance status, or ineligibility for surgery, minimally invasive strategies offer attractive alternative treatments such as radiotherapy or thermal ablation. Several methods of the latter exist, including RFA, MTA, and cryoablation.\(^{19}\) Computer tomography offers the most accurate image-guidance technique for RFA of lung lesions, while also allowing for quick needle placement.\(^{19}\) Local tumor control can be achieved in 90% of cases.\(^{20}\) Treatment of tumors less than 2 cm had the best success rate, with recurrences between 4% and 22% in long term follow-up, whereas larger tumors had high recurrence rates, with reports ranging from 65% to 100% in tumors greater than 3.5 cm.\(^{21}\) Comparison with surgery in large-scale randomized controlled trials, however, is needed.

One of the main predictors of treatment success is ablation safety margins. For multi-tined needle arrays, a safety margin greater than 10 mm was associated with a reduction from 30% to 10% recurrence rate,\(^{22}\) highlighting the necessity for a sufficient ablation margin. Thermal ablation is currently reserved for inoperable lung tumors, but an extension to early stages is being explored. In terms of ablative technologies, while RFA has been studied more widely, some advantages exist also for MTA. As with liver cancer, proximity to major vessels during thermal ablation has been also reported as a negative predictive factor in the lung, likely due to the heat-sink effect.\(^{23}\) This effect is reduced with MTA compared to RFA.\(^{19}\)

1.2. Colorectal Cancer Liver Metastasis

With colorectal cancer (CRC) being the third most frequent cancer type, around 50% of patients develop hepatic metastases during the course of their disease.\(^{18}\) With recent high-level evidence that thermal ablative technologies for CRC liver metastasis have improved overall survival compared to palliative chemotherapy, thermal ablative technology has become an important treatment option for patients with unresectable diseases.\(^{24}\) Current indications for thermal ablative treatment for colorectal liver metastasis include unresectable liver lesions or patients unfit for surgical resection.\(^{25}\) Thermal ablation for CRC liver metastasis is not currently recommended for lesions greater than 5 cm, due to the greater chance for incomplete tumor ablation, which leads to most guidelines recommending an upper limit of 3 cm.\(^{25}\) Other contra-indications to thermal ablation include coagulopathy, diffuse liver disease (more than 8 lesions), unfavorable tumor location, or extra-hepatic disease.\(^{26}\) The role of thermal ablative treatments for liver cancer is evolving. While its role in the treatment of unresectable liver metastasis has been well established with recent successful large clinical trials,\(^{24}\) there are now ongoing trials comparing thermal ablation to liver resections in small liver metastases.\(^{27}\)
1.3. Thermal Ablation via Endoscopic Methods for the Treatment of Early Esophageal Neoplasms

The RFA has found also application in the treatment of Barrett’s esophagus (a pre-malignant esophageal lesion) and early esophageal neoplasm. It allows for treatment of lesions confined to and not extending beyond the lamina propria mucosae. These lesions have a low risk of lymph node metastasis, which allows for organ-sparing and endoscopic treatment. Historically, these lesions would have required an esophagectomy, an operation associated with significant perioperative morbidity and mortality. Recent studies have demonstrated comparable oncological outcomes between endoscopic treatment methods and traditional surgery. Precise depth control during endoscopic treatment is not only important in ensuring good oncological treatment, but also to help prevent esophageal strictures that can arise due to collateral damage to the closely adjacent muscular layers. The RFA has emerged as the treatment of choice for Barrett’s esophagus and early esophageal neoplasms due to its lower stricture rate when compared to other endoscopic treatment modalities. The average remission rate was 84%, while stricture rates were reported between 0% and 28%. 

1.4. Novel Thermal Ablation Techniques and Central Nervous System Tumors

While RFA and MTA have pioneered thermal therapy and are still clinically used widely, they lack the required precise spatial control highlighted just above. Various factors can influence their efficiency, including tumor size, location, and proximity to other vital structures or vessels, as well as devices used. Different devices have different shapes and sizes of ablation zones that depend on the employed power and duration. Knowledge of these parameters prior to treatment is vital. More specifically, RFA can suffer from asymmetric treatment volumes, due to current traveling along the path of least resistance. The MTA, on the other hand, has the drawback of very limited control over the area of effect due to the applied high temperatures. The combination of thermometry methods with either technique is not straightforward, hindering feedback-control integration. This restricts the application of thermal ablation to solid tumors with simple geometry and unrestricted boundaries. Furthermore, larger tumors (diameter > 30 mm) are problematic. Sensitive tissue close to the lesion limits applicability, as RFA and MT ablation treatments require safety margins of 5–10 mm. 

As a result, more precise and controllable heating strategies have been sought for and developed. Of these, laser interstitial thermal therapy (LITT) has gained a prominent status. It heats the diseased tissue by laser light with wavelengths typically in the near-infrared window. A thin optical fiber is endoscopically inserted into the tumor and the heating procedure is followed via magnetic resonance thermometry. The LITT has found applications in treating prostate and brain tumors. The ability to visualize real-time temperature changes in deep regions with the help of MRI thermometry, allows for precise, near surgical ablation in commonly inaccessible areas, such as the brain. Spatial precision is of the utmost importance when treating brain tumors, as damage to surrounding tissues can lead to permanent neurological consequences. Two commercially available systems exist for the use of LITT in neurosurgery, both using diode lasers with probe diameters between 1.1 and 1.6 mm. Current indications for LITT in neurosurgery include neoplastic disease, with glioblastoma multiforme being the most widely studied, radiation necrosis, and epilepsy. Although LITT shows improved spatial control over RFA or MTA due to the observation capability, the remaining dependency on the exact fiber placement still limits its useability. Depending on the exact geometry of the lesion, several fiber locations are necessary, which increases the invasiveness of the procedure. This highlights, even more, the lack of suitable alternatives and the need for therapies with high spatial control.
2. Clinical Thermometry Methods: The Problem of Temperature Control

In order to advance thermal therapies, the precise spatiotemporal observation (i.e., thermometry) and exact control of the tissue temperature profile are critical. Various thermometry techniques based on currently used imaging modalities are already clinically available and occasionally used. Here, the most common and promising (i.e., thermometry via MRI, photoacoustic imaging (PA), ultra-sound (US), and computer tomography (CT)) are compared quantitatively with respect to their spatial and temperature resolution.

There have been significant efforts over the last decade to improve the planning and outcome of thermal treatments via various simulation approaches.[34] Here, we numerically investigate a simple solid tumor model under heating with Pennes’ bio-heat equation,[35] which shall give insight into the importance of thermometry accuracy and heating control.

A single-dimensional model in Cartesian coordinates is assumed. Figure 2a depicts a schematic of the analyzed scenario. We assume a constant temperature ($T_{\text{surface}}$) at the tumor surface including the safety margin ($\Delta_1$). The latter corresponds to the adjacent tissue volume, which is included in all therapies to account for diffuse tumor boundaries. Blood perfusion as well as metabolic effects, which are highly patient and tumor-specific,[36] are neglected for simplicity. Nevertheless, these assumptions neither affect the temperature profile outside the tumor nor the resulting treatment margin ($\Delta_2$), which is given by the constant boundary conditions $T_{\text{surface}}$ and $T_\infty$. At sufficient distance from the tumor surface (> 15 mm) the temperature is unaffected by the heating procedure and remains at 37 °C. In between, a temperature profile develops by heat transfer, which evolves over time as indicated. Temperatures below 40 °C ($T_{\text{safety}}$) ensure no tissue harm even during long exposure time and are therefore chosen as a safety zone. The tissue volume exposed to temperatures above $T_{\text{safety}}$ and outside $\Delta_1$ is depicted as treatment margin ($\Delta_2$) and corresponds to the uncertainty caused by unavoidable heat transfer. This thickness of the treatment margin, $\Delta_2$, was computed as a function of $T_{\text{surface}}$ for treatment times $t = 1$, 10, and 30 min, and depicted in Figure 2b (see Supporting Information for details). The treatment margin ($\Delta_2$) increases for increasing $T_{\text{surface}}$, due to a bigger temperature difference to the surrounding, as well as
as for longer treatment times following increased heat transfer from the treated tumors. A realistic assumption of $T_{\text{surface}} = 45$ °C and $t = 10$ min results in a treatment margin ($\Delta t$) of $\approx 11$ mm (Figure 2c, indicated in orange). This value is distinctively lower than safety margins currently assumed during most surgical resections of tumors (see Table 1). This highlights the tremendous importance of exact temperature control. Current thermal therapies via RFA or MTA include a safety margin of 5–10 mm, where, however, the inclusion of treatment margins remains unclear, especially as a function of treatment temperature.

Precise heating control requires monitoring of temperature. To this end, Figure 2c shows the treatment margin $\Delta t$, accounting for the spatial and temperature resolution of different thermometry methods (MRI, PA, US, CT; see Table S2, Supporting Information) in comparison to its exact value (orange bar and broken line). Temporal resolution was not considered, as it does not have an immediate effect on a feedback control system without perturbations. MRI thermometry shows the highest resolution, with an uncertainty of roughly 2 mm to the actual position of the treatment margin ($\Delta t$). Thermometry via PA imaging shows a slightly lower resolution, followed by ultrasound and CT-based methods. All depicted uncertainties in determining $\Delta t$ by thermometry, however, are much lower than the actual value of $\Delta t$ ($\approx 11$ mm). It is therefore not so much the accurate temperature measurement, but rather the precise control of temperature based on measurements that represents the biggest hurdle in thermal treatments. Currently available thermometry methods (e.g., via MRI) yield temperature distributions at sufficient detail for clinically successful thermal therapies. This effect gets even more pronounced for longer treatment times and higher treatment temperatures. Only for very small values of $t$ or $T_{\text{surface}}$, close to $T_{\text{safe}}$ (40 °C), the thermometry resolution could be a potentially limiting factor. These two heating variables (i.e., $t$ and $T_{\text{surface}}$), however, are inversely proportional, as lower treatment temperatures typically require longer treatment times.

Further model components such as 3D boundaries can influence the detailed temperature profile. Blood perfusion in diseased or surrounding healthy tissue can decrease the treatment margins. However, it can also lead to asymmetric temperature distributions and inhomogeneous heating, as shown already in the 90’s. Overall, blood perfusion strongly depends on the exact geometry and location of the vessels, which is highly tumor-specific. Although important for individual treatment planning, it will not diminish the overarching problem of missing heating control illustrated here.

### 3. Particle-Based Controlled Heating

This lack of tissue-selectivity during thermal treatment is its bottleneck today. To overcome it nanoparticles have been introduced, which shall convert energy that is selectively delivered to the target site into heat. As a result, the temperature profile is governed by the exact location of nanoparticles (Figure 3a–c) that can be tailored to specifically absorb the provided energy with much higher efficiency than the tissue itself. That way much lower energy dosages are sufficient and harmless to particle-free tissues. Simulations have shown that using gold nanoparticles for photothermal treatments enables the containment of the temperature to a much narrower field than using laser irradiation only, also in the presence of large blood vessels that act as heat sinks. This could be confirmed during in vivo photothermal experiments where the enhanced optical extinction confined the source of the resultant heat to nanoparticle-containing tissue. This resulted in a steep temperature gradient at the tumor boundary that confines thermal damage to the target tissue.

Therefore, nanoparticle-based thermal therapy has the prospect to translate to improved clinical outcomes while minimizing side-effects commonly observed in other focal ablation modalities caused by ablation of non-targeted tissue. Target tissue can be heated up within minutes with superior control, which opens up pathways to time-dependent heating protocols (e.g., intermittent heating). This allows for highly precise heating strategies, required for the treatment of tumors with large and/or complex geometry, as well as, tumor treatment close to essential body compounds.

The two most common groups are photothermal nanoparticles (typically based on plasmonic gold) or cheaper alternatives such as TiN coated with a SiO$_2$ shell that strongly absorb near-infrared light from a laser (Figure 3d), and magnetic nanoparticles (e.g., ferrites where heating efficiency is determined by the coercivity that can be heated under a rapidly oscillating magnetic field (Figure 3e). In principle, both can be combined with any thermometry method. Currently, invasive fiber-optic probes are still the gold-standard for point measurements while MRI thermometry has been the preferred option for 3D thermal imaging (Figure 3f). Additionally, particles themselves can also be employed for control over thermal heating in the form of actively-controlled heating (Figure 3g) or self-limiting (Figure 3h) systems.

To highlight the advantages of nanotechnology in thermal therapies, three examples will be given where nanoparticle-based thermal therapy has been applied already in vivo as the current standards of care were not applicable.

- **Locally Recurrent Prostate Cancer following Prior Radiotherapy in Humans**

In the absence of an extant standard treatment for recurrent prostate cancer, the only standard option for patients would be salvage radical prostatectomy. Jordan and coworkers employed magnetic nanoparticle heating to destroy the tumors, reporting promising results with increased quality of life.

- **Canine Transmissible Venereal Tumor as Proxy for Orthotopic Brain Metastasis**

Schwartz et al. reported a proof-of-concept for photothermal therapy using gold nanoshells. Brain tumors with diameters below 3 cm are typically treated using stereotactic radiosurgery but complications include early treatment-induced edema, seizures and delayed radiation necrosis. Following intravenous injection of gold nanoshells, they demonstrated effective and selective therapy with minimal thermal damage to normal brain tissue.

- **Prostate Tumors in Humans**

A clinical trial using intravenously injected gold nanoshells for photothermal ablation of prostate tumors was reported by Rastinehad et al. They achieved ultrafocal photothermal ablation of cancerous tumors that are located near several vital structures such as urethra and neurovascular bundle, thereby
Figure 3. Particle-based controlled heating: Particles are heated under temperature monitoring to enable feedback control. a–c) Methods for local heat delivery, d,e) heating mechanism, f–h), and local temperature monitoring, which in combination lead to i) precisely controlled temperature in the tumor and its vicinity.

substantially reducing risks for deleterious treatment-related side effects.

However, using particle-based approaches for controlled thermal therapy, although highly promising, comes with its own challenges. These include the delivery of particles to the target site,[53] accurate and localized heating, and adequate control mechanisms during heating. In the following, the various particle-based strategies will be introduced in detail and outstanding examples highlighted, while also discussing their advantages and limitations.

3.1. Targeting Efficiency

To achieve selective heating and avoid unwanted damage to healthy tissue, it is crucial to have a sufficiently high concentration of nanoparticles at the tumor site. However, as with all particle-based strategies to fight cancer, the selective and targeted delivery of nanoparticles into diseased tissues remains one of the biggest challenges in nanomedicine.[54] Nanoparticles can be injected either intravenously or directly into a tumor, resulting in high local concentrations that are required in cases like magnetic particle heating. However, direct intratumoral injection is not always possible (e.g., small metastatic tumor growths), is invasive, and generally does not cover tumors adequately.[55] In brain tumors, particle distributions were found to be restricted to the sites of injection.[56] Similarly, in a study of breast tumors, areas of under-dosage (for sufficient heating) were identified after intratumoral injection, predominantly at tumor peripheries,[57] at least partially caused by wash-out of particles. In contrast, Huang et al.[58] could not even detect any nanoparticles (single-walled carbon nanotubes) 1 mm around the apparent edge of the tumor in mice after intratumoral injection. Still, intratumoral injection via multiple injection sites is currently the most promising approach if high concentrations are required. However, inhomogeneous particle distribution can still only be partially improved through this approach.[59] Additionally, the repeated needle penetration may also increase the risk of local tumor spread through metastasis.[60]

In contrast, intravenous injections lead to more homogeneous distributions within the tumor, but at lower concentrations. Besides being less invasive, it also enables to cover irregularly shaped tumors and metastasis more precisely, even though the concentrations in the tumor centers are lower due to carcinomas’ poor central circulation.[61] It has been found that after intravenous injection of gold nanoparticles in mice about ≈10 times more particles accumulated in the tumors than in the surrounding tissue,[61] which was assigned to the enhanced
permeability and retention (EPR) effect. Similarly, in a currently running clinical trial\textsuperscript{52} for photothermal therapy using gold nanoparticles for human prostate cancers, the particle concentration at the tumor sites was $\pm 3.5$ times higher than in surrounding tissues.\textsuperscript{62} However, the overall efficiency delivery of intravenously injected particles remains very low (0.7\%),\textsuperscript{54} which led to severe doubts of the importance of the EPR effect for nanoparticle targeting. Still, the concentrations in the tumor centers are lower due to the carcinomas' poor central circulation.\textsuperscript{61} Advantageously, this can cut off blood supply to central tumor regions.\textsuperscript{35}

The effect of differently distributed nanoparticles on photothermal heating effect in skin tumors was numerically investigated by Soni et al.\textsuperscript{63} Three different configurations were tested: Uniform distribution, highest concentration in tumor center (simulating intratumoral injection), and highest concentration in the tumor periphery (simulating intravenous injection). Interestingly, when nanoparticles were located in the periphery of the tumor, the most homogeneous (and therefore effective) temperature increase could be observed, while a single particle deposit in the center of the tumor was least effective. Experimentally, similar observations have been made using magnetic nanoparticles.\textsuperscript{64} Following intratumoral injection, the particle distribution could be improved using a specific tumor-targeting peptide, which lead to better antitumor efficiency attributed to the more uniform heat delivery.

For photothermal nanoparticle therapy, the spatial treatment control can be increased by focusing the laser light into the area of interest, meaning that off-target particles should not be heated up. This is in contrast to magnetic particle heating, where focused energy delivery is still in development and thus rarely applied. As a result, in almost every magnetic particle heating application particles have been injected intratumorally to reach the required high local concentrations. A variation has been reported by Hainfeld and Huang,\textsuperscript{55} who injected iron oxide nanoparticles intravenously and only inserted the tumor-bearing leg of a mouse into the magnetic field, keeping off-target particle accumulations (e.g., in the liver) “inactive.”

### 3.2. Magnetic Particle Heating

#### 3.2.1. Conventional Control in Magnetic Particle Heating

Magnetic iron oxide nanoparticles for thermal treatment using an oscillating magnetic field have been developed for several decades. However, the precise temperature control by conventional methods remains challenging, especially since MRI thermometry cannot be easily combined with magnetic particle heating. In 2007, Johannsen et al.\textsuperscript{50} treated prostate cancer patients using ferrite particles. Based on CT-imaging, they developed a 3D model for thermometry, which was calibrated and verified using various invasive optical fibers as temperature sensors. While they achieved reasonable agreement between invasive and calculated temperature in the target region (1.1 °C deviation). The calculated temperature, however, was too high near the floor of the bladder (due to the neglect of convection) and too low toward the perineum, most likely due to higher power deposition toward the superficial (skin) region despite the absence of nanoparticles there.

#### 3.2.2. Self-Limiting Magnetic Particle Heating

A crude method of controlled magnetic particle heating is the use of particles containing a self-limiting heating property. Above a certain threshold, such particles will lose their heating capacity and thus avoid overheating (Figure 4, dashed line). In the case of magnetic nanoparticles for thermal therapy, this is typically achieved by tuning the Curie temperature,\textsuperscript{65} that is, the temperature where their magnetization is lost.

The search for suitable magnetic materials is ongoing since common magnetic materials (e.g., Fe$_2$O$_3$) have a Curie temperature that is much too high. Therefore, the focus has been on manganite perovskites and spinel ferrites.\textsuperscript{65} It has been shown that the exact particle composition and size can affect the Curie temperature.\textsuperscript{66} Still, reports on in vivo applications of self-limited magnetic particle heating are scarce. One of the first were by Saito et al.\textsuperscript{67} who employed 100 μm thermosensitive ferromagnetic particles (a mixture of Fe$_2$O$_3$, CuO, ZnO, and MgO, injected 500 mg intratumorally) and achieved good heating limited at 43°C. After repeated heat treatment, tumor growth could be suppressed, though not completely. While they report good spatial selectivity (only heating of the tumor area, as controlled by optical fiber thermoprobes), the required therapy time was relatively long (>30 min), with around 7 min to reach 43 °C. Similarly, Herynek et al.\textsuperscript{68} used perovskite nanoparticles (La$_{0.75}$Sr$_{0.25}$MnO$_3$, $T_{\text{curie}} = 66–74$ °C). Recently, Wang et al.\textsuperscript{69} proposed a new concept for self-limited magnetic particles; instead of tuning the Curie temperature, superparamagnetic nanoparticles (SiO$_2$-coated Fe$_3$O$_4$, mean diameter = 150 nm) are introduced in a phase change material with a high phase transition enthalpy in the range of 41–47 °C. Therefore, the heating is slowed down significantly within this region.

#### 3.2.3. Challenges in Magnetic Particle Heating

For magnetic particle heating, there are no limitations regarding penetration depth (as in MRI). The selective local delivery of heat through high gradient magnetic fields was investigated and a potential localization within a radius of 2.3 mm was described.\textsuperscript{70} In combination with improved particle delivery strategies, such an approach becomes highly promising for localized thermal therapies. For self-limited systems, the particles have both heating and temperature control functionality. As the particles are supposed to deliver damaging heat exclusively to the tumor, they should be localized in the tumor tissue. Ideally, the heating threshold is tuned precisely to a temperature that is harmful to tumor tissues while avoiding damage to healthy tissue. Fortunately, cancerous tissue is more susceptible to irreversible heat-damage in the region of 40–43 °C.\textsuperscript{71} Thus, the requirements for precise targeting are lowered, as even heating particles in healthy tissue would not cause irreversible damage.

Proper control of heating depends on the accuracy of temperature measurements. An uncertainty in the range of 1 °C is sufficient, as highlighted above. Considering that typical particle heating treatments can last anywhere from 3 to 30 min, a maximum sampling time of $\approx 10$ s should be effective. The time required for the switch from “heating” to “non-heating” is hardly ever reported. The temperature threshold is usually not a “sharp”
transition but occurs over a relatively broad range, which results in long required times to reach therapeutic temperatures if the transition temperature is close to the treatment threshold.[72] Considering the difficulty already to precisely tune the Curie temperature for magnetic particles (e.g., by material composition) or the transition temperature for optical self-limiting systems, it seems unlikely to achieve a very precise control with these systems and therefore represents one of the major drawbacks. Additionally, these systems lack flexibility with characteristics that cannot be adapted on-the-fly to unforeseen events (e.g., insufficient particle concentration).[68]

3.3. Plasmonic Photothermal Heating

3.3.1. Conventional Control in Photothermal Therapy

Photothermal therapy has gained interest with the introduction and refinement of strongly light-absorbing plasmonic nanoparticles. In particular, the groups of West and Halas have pioneered the field with the development of gold nanoshells and their application for thermal treatment. A first proof-of-concept was given for tumors in mice[73] in 2003, followed by brain tumors in canines,[143] and recently in clinical trials for prostate tumors.[53] They measured the temperature distribution in 3D using MRI thermometry based on the proton resonance frequency shift. While this led to accurate results, it was not used to actively control the therapy in form of a feedback loop, but rather to more or less find suitable operating conditions in terms of particle concentration and (fixed) laser power. Similarly, Meng et al.[74] produced multifunctional nanoparticles (NaBiF4:Gd@PDA@PEG) acting both as photothermal agents and MRI T1-contrast agents. Combined with MRI thermometry, they could image the nanoparticle distribution and assess the 3D temperature distribution during therapy of a superficial tumor with a time resolution of 19 s and an accuracy of 0.1 K.

3.3.2. Self-Limiting Photothermal Therapy

For optically active nanoparticles, self-limiting systems have not yet been as established as for magnetic particle heating. Materials with low crystal phase transition temperatures (mostly VO2)[75] have been suggested[76] as the resulting change in the refractive index could shift a narrow extinction peak away from the laser wavelength, and thus self-limit the heating. However, alternative methods based on reversible thermochromism have been reported recently. They rely on the phase transition (melting) of certain components. Such systems (e.g., iodine-loaded acetylated amylose nanohelix clusters[77] or leuco dye-developer solvent systems[78]) enable precise turning of the transition temperature to 45 °C, and thus effectively controlled photothermal treatment of tumors in vivo.

3.3.3. Challenges in Photothermal Therapy

In contrast to magnetic fields, light energy can be delivered more easily in a highly localized fashion by focusing. Still, the light-tissue interaction heavily influences performance and restricts the penetration depth. Shifting the spectral operating range from the visible region to longer wavelengths (NIR-I: 750–950 nm, NIR-II: 1000–1400 nm) can drastically reduce absorption and scattering by biological tissue.[79] Therefore, advances in photothermal agent development have focused on nanoparticles operating in these regions. Thus, photothermal therapy is mostly applied when the light only has to penetrate through thin layers of tissue, for example for the therapy of skin.
cancer. Moreover, since light energy can be easily delivered using fiber optics, it is also applicable for the use near body cavities, as in the case of prostate cancer.\cite{52}

### 3.4. Particle-Based Actively-Controlled Systems

The drawbacks of self-limited particle-based heating methods can be overcome using advanced systems with particles that act as thermometers. To fully enable their potential\cite{80} in thermal therapies, these thermometer-particles need to be at the same location as the nanoheaters, which can only truly be achieved when these two functionalities are coupled in a single nanosystem. Therefore, this section focuses on combined systems only, whereas reviews on particles for thermometry have been discussed by others.\cite{81} While there are emerging methods for particle-based thermometry\cite{82} or single particle thermometry using a nanopipette\cite{83}, by far the most prominent are fluorescent thermometers that make use of the temperature-induced spectral changes. While in principle any temperature-induced change could be used as a read-out signal, such systems typically make use of the intensity of a single peak, the ratio of two emitted peaks,\cite{84} or a shift of the peak.\cite{85}

The simplest approach to combined thermometry and heating are single-core systems that already contain both functionalities. In theory, this is the case for any thermometric system with high absorption. However, so far in vivo thermal therapy applications have only been demonstrated using heavily doped LaF$_3$:Nd\cite{86} and PbS/Cds/ZnS quantum dots.\cite{87} For LaF$_3$:Nd, a ratiometric read-out was used, while for the quantum dots only the relative change in emission intensity (during treatment time) was used. The quantum dots were characterized by higher thermal sensitivity (1%/K), stronger absorption and operation in the preferred NIR-II window, yet the uncertainty in temperature measurement remained similar at $\pm 1.1$ K.

Zhu et al.\cite{88} synthesized a more complex nanosystem consisting of an upconversion core (NaLuF$_4$:Yb,Er), and a strongly absorbing carbon shell. Due to the spectral properties of the two components, two separate lasers (730 and 980 nm) were employed.

Alternatively, heating and thermometry functionalities can be combined by encapsulating two separate kinds of particles in a larger structure. Rocha\cite{89} demonstrated this by combining gold nanorods and LaF$_3$:Nd particles encapsulated in a poly(lactic-co-glycolic acid) (PLGA) structure. Similarly, this concept was expanded by Ortgies et al.\cite{90} to include magnetic particles for heating and LaF$_3$:Nd for thermometry, encapsulated in PLGA structure.

### 3.4.1. Challenges in Particle-Based Actively-Controlled Systems

For particle-based controlled heating the requirements with respect to particle delivery are not as stringent. As long as sensing particles are present at the site of interest, they can provide feedback. However, ideally, they are present both in tumors and their close surroundings to achieve better temperature control. In this regard, it might even be of benefit that intravenously delivered nanoparticles tend to accumulate at the surrounding of the tumors, thus at the most crucial location in terms of temperature. On the negative side, systems where the heating and thermometry are both controlled using the same laser are less flexible.

Actively particle-controlled systems allow typically very fast (ms to s) feedback since it is based on optical emission. While temperature uncertainty under ideal conditions can reach very low values ($\approx 0.05$ K),\cite{91} this is reduced drastically under operating conditions.\cite{85} Most of the time the uncertainty is related to the signal quality/strength, which is to the signal quality/strength, that is deteriorated by low particle concentration or thick tissue layers in the optical path. Therefore, temperature uncertainties in more realistic scenarios are around 0.5–1 K.\cite{92} Still, it should be pointed out that this is clearly high enough and thus does not represent the major bottleneck in controlled thermal therapy. Another limitation is that for fluorescent nanothermometers, typically only the combined signal is collected from a single point. Thus, more sophisticated equipment is necessary to reach 2D temperature maps.\cite{93} While theoretically also 3D thermal mapping would be possible, this has not yet been shown in a realistic scenario.

### 4. Concluding Remarks

Thermal therapies of neoplastic tissues have become attractive alternatives in oncological treatments of lung or liver tumors. The main reason for this success lies in the limitation of commonly used methods, including surgery, radiotherapy, and chemotherapy, which often suffer from accessibility or significant side effects. Margin control during surgery and radiotherapy can lead to significant collateral damage, which represents probably the biggest advantage of thermal therapies. This is most evident in thermal therapies for brain tumors, where precise treatment control is the prerequisite for success. Ultimately, by using thermal techniques over traditional oncological treatments, safety and treatment margins can potentially be reduced, and by extension collateral damage. Interestingly, however, this potential in spatial control has not been fully utilized for most tumor types; required margins during surgical resection and thermal treatments are comparable for most tumor types. This is especially surprising, as temperature distributions can be monitored during the procedure with fair resolution using existing clinical imaging techniques, such as MRI or CT. This hints to the main issue we highlight in this work: Temperature monitoring is ineffective without precise heating control. Existing thermometry methods have distinctly lower uncertainties than the spatial spreading of temperature profiles with time due to thermal conduction. Therefore, research has to focus on strategies to control these temperature profiles and reduce safety and treatment margins during clinical scenarios.

This opens up an immense opportunity for solutions based on nanotechnology (Figure 3). Various types of nanoparticles can locally deliver heat after excitation via light or magnetic fields. This enables, in theory, temperature control at scales lower than the uncertainty of thermometry methods and is dictated mostly by the exact position of the structures or localization of the excitation medium (i.e., light intensity, magnetic field strength). Self-limiting materials, which benefit from the higher
heat-sensitivity of cancerous compared to healthy cells, show further potential for increased treatment control. At the same time, thermometry methods based on nanoparticles have been proposed for high-resolution temperature monitoring. The success of nanoparticle-based heating and thermometry will ultimately depend on the targeting efficiency of the structures to the diseased site.

Over the last decade, however, tremendous effort has instead been made to optimize heating and thermometry efficiencies through tedious material optimization. The gain of this work, unfortunately, is limited. No faster heating strategies or more precise temperature measurements alone will lead to the required minimization of treatment margins, which represents the main issue of current clinical thermal therapies. We were able to highlight this misconception through our simple thermal therapy example described in Figure 2, which shows the efficiency of current clinically available thermometry methods. As a result, the emphasis has to be put on the joined improvements of heating strategies and temperature measurements. Research focus on the feedback control systems should lead the way forward to the goal of increased success of thermal therapies.

Without this shift of emphasis, thermal therapies using nanoparticle-based approaches will remain in the shadow of more established techniques, such as surgery or radiotherapy. Current clinical thermal therapies still are, despite their extensive history, mostly only salvage or adjuvant solutions to more common therapeutic approaches. Instead, they should be developed as an alternative to current standards of care in the primary setting to ensure wide clinical acceptance.

Specifically, we suggest the following four tackling points for research to ensure the success of thermal therapeutic approaches in clinics in the near future: 1) Increasing targeting efficiency of nanoparticles to diseased site: Current delivery strategies only show moderate success, as on average only 0.7% of intravenously injected particles reach the cancerous site.\(^{[54]}\) At the same time, particle concentrations in the order of 70 mg mL\(^{-1}\) of tumor are required for a sufficient magnetic particle heating effect.\(^{[94]}\) This discrepancy is the main limitation throughout all of nanomedicine today. A higher control in localization of the nanoparticulate heating agents would drastically decrease treatment- as well as safety-margins. 2) Increasing spatial control over energy delivery used for heating: This approach has shown first success in magnetic particle heating via high gradient fields.\(^{[70]}\) The combination with nanoparticle heating agents gives this approach more flexibility and is therefore expected to lead to drastic improvements compared to current margins of thermal therapies. 3) Expanding temperature control and monitoring strategies to 3D systems: Current techniques are frequently investigated only in 1D or 2D environments, which strongly limits the significance of such reports. Carcinogenic tissue commonly is of complex 3D architecture, often with diffuse boundaries. This issue has led to the development of novel techniques to assess boundaries during surgical excision\(^{[93]}\) and should be also considered for thermal treatments. 4) Ensuring applicability in clinical environments: Various therapeutic, as well as diagnostic techniques, have not found clinical acceptance despite their regulatory approvals. This is a result of various factors, such as missing reproducibility, complexity in handling, laborious integrability into existing techniques, and high costs. These issues have to be tackled already during early development stages, as subsequent changes are expensive.

**Supporting Information**

Supporting Information is available from the Wiley Online Library or from the author.

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**Conflict of Interest**

The authors declare no conflict of interest.

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