Focal therapy for localized cancer

a patent review

Bloemberg, Jette; Van Riel, Luigi; Dodou, Dimitra; Breedveld, Paul

DOI
10.1080/17434440.2021.1943360

Publication date
2021

Document Version
Final published version

Published in
Expert Review of Medical Devices

Expert Review of Medical Devices

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierd20

Focal therapy for localized cancer: a patent review

Jette Bloemberg, Luigi Van Riel, Dimitra Dodou & Paul Breedveld

To cite this article: Jette Bloemberg, Luigi Van Riel, Dimitra Dodou & Paul Breedveld (2021) Focal therapy for localized cancer: a patent review, Expert Review of Medical Devices, 18:8, 751-769, DOI: 10.1080/17434440.2021.1943360

To link to this article: https://doi.org/10.1080/17434440.2021.1943360

Published online: 28 Jun 2021.

EXPERT REVIEW OF MEDICAL DEVICES
2021, VOL. 18, NO. 8, 751–769
https://doi.org/10.1080/17434440.2021.1943360

Taylor & Francis
Taylor & Francis Group

REVIEW

Focal therapy for localized cancer: a patent review

Jette Bloemberg [a], Luigi Van Riel [b], Dimitra Dodou [a] and Paul Breedveld [a]

[a]Bio-Inspired Technology Group (BITE), Department of Biomechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands; [b]Department of Urology and the Department of Biomedical Engineering & Physics, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

ABSTRACT

Introduction: Conventional cancer treatments such as radical surgery and systemic therapy targeting the organ or organ system might have side effects because of damage to the surrounding tissue. For this reason, there is a need for new instruments that focally treat cancer.

Areas covered: This review provides a comprehensive overview of the patent literature on minimally and noninvasive focal therapy instruments to treat localized cancer. The medical section of the Google Patents database was scanned, and 128 patents on focal therapy instruments published in the last two decades (2000–2021) were retrieved and classified. The classification is based on the treatment target (cancer cell or network of cancer cells), treatment purpose (destroy the cancerous structure or disable its function), and treatment means (energy, matter, or a combination of both).

Expert opinion: We found patents describing instruments for all groups, except for the instruments that destroy a cancer cell network structure by applying matter (e.g. particles) to the network. The description of the different treatment types may serve as a source of inspiration for new focal therapy instruments to treat localized cancer.

ARTICLE HISTORY
Received 12 March 2021
Accepted 9 June 2021

KEYWORDS
Cancer; focal therapy; instrument design; localized; review

1. Introduction

1.1. Background

Patients diagnosed with cancer encounter a dilemma: the choice of the type of treatment. There is a wide range of possible cancer treatment modalities, including radical surgery, radiotherapy, and systemic treatment, such as chemotherapy, hormonal therapy, or immunotherapy [1]. Treatments targeted at the organ or the organ system might have side effects because of damage to the surrounding tissue [1–3]. A strategy to overcome this problem is to focus the treatment on the cancer cells (i.e. the lesion), thereby preserving noncancerous tissue, a method called focal therapy [4–6].

There is no consensus in the literature on the exact definition of focal therapy. In this review, we defined focal therapy as a minimally or noninvasive therapy that focuses on the localized killing of cancer cells without resecting them. The remaining dead cancer cells are subsequently resorbed via normal body mechanisms [7]. Focal therapy is possible when the cancer is detected at an early stage because then the cancer cells are still positioned locally at an organ-confined space [8–10].

The localized killing by focal therapy aims at different organizational levels of the body as compared to conventional treatment such as systemic therapy. The structural hierarchy of the human anatomy consists of distinct levels of organization that increase in complexity: the cellular, tissue, organ, organ system, and organismal level [11]. The cancer tissue/network comprises the cancer cells and their vascular network for the supply of oxygen and nutrients and the removal of waste products, essential for the cancer progression [12]. Every level of organization is characterized by its anatomy (the structure) and physiology (the function), both being essential for its existence [11]. Focal therapy targets either the tissue or the cell level, whereas radical surgery targets the cancer cell network and a margin of normal tissue surrounding it (e.g. the whole organ in radical prostatectomy), and systemic therapy targets the organ system [13–15].

1.2. Problem definition

Cancer treatments such as radical surgery and systemic therapy damage not only the cancer cells but also the surrounding tissue, leading to undesirable side effects [1–3]. The damage might lead to functional problems. For example, prostate cancer patients who receive standard radical treatment, including radical prostatectomy or radiotherapy, are at risk of side effects that impair urinary, sexual, or bowel function [16–18].

Focal cancer treatment reduces the risk of side effects. Focal treatment is possible when the cancer is unifocal. Recently, there is an increasing interest in focally treating unifocal prostate cancer [3]. The anatomy and physiology of both the cancer cell and network of cancer cells facilitate a wide range of focal therapy instruments. Focal therapy instruments comprise a collection of instruments using different means (e.g. energy such as ultrasound waves) to target various properties of the lesion to cause local cell death [6,19]. A clear classification of focal therapy instruments, described in the patent literature, would serve as an overview of the

CONTACT Jette Bloemberg jettebloemberg@gmail.com Department of Biomechanical Engineering, Faculty of Mechanical, Maritime and Materials Engineering, Delft University of Technology, Delft, The Netherlands

treatment types applied by focal therapy instruments. This study focuses on patent literature because it provides insights into the future directions of the technologies applied by the instruments described in patents. To our knowledge, a comprehensive overview of the patent literature on focal therapy instruments to treat localized cancer is not yet available.

1.3. Goal and structure

This study presents a comprehensive overview of the patent literature on focal therapy instruments to treat localized cancer. We decided to focus on focal treatment instruments for unifocal cancer in general, the working principle of instruments to treat for example prostate cancer could also be of interest for the treatment of unifocal cancers in other organs such as the breast, kidney, or liver. An overview of the patent literature on focal therapy instruments provides insights into the future directions of the technologies applied by these instruments. The relevant patents were classified based on their treatment target, purpose, and means. First, the method of the patent search on focal therapy instruments is described in Section 2. Next, the instruments found in the patents are categorized and described. The classification of the focal therapy instruments targeting the individual cancer cells is described in Section 3. The classification of the focal therapy instruments targeting the network of cancer cells is described in Section 4. Then, the commercially available instruments are discussed in Section 5. The types of treatment and the instruments are discussed in relation to the temporal distribution of the classified patents in Section 6. Section 7 presents the conclusion and Section 8 provides our expert commentary on this topic.

2. Method

2.1. Patent search method

A search within the patent literature for medical instruments used for focal therapy to treat localized cancer was conducted using the Google Patents database (accessed June 2021). Our search query was a Boolean search term consisting of a combination of keywords related to (1) the focal character of the treatment, (2) the type of treatment, (3) the pathology to be treated, and (4) the treatment tool and its design (Figure 1(a)).

We looked for the above-mentioned combination of search terms at the claims, title, and abstract of the patents. We restricted our search to patents linked to the Patent Cooperation Treaty (PCT), by using the prefix 'WO' in the search term. Furthermore, we restricted our patent literature search to patents published after 1 January 2000. Lastly, we restricted our search within the medical field with the World Intellectual Property Organization (WIPO) code 'A61,' which corresponds to the medical or veterinary science and hygiene class of human necessities. This class contains several subclasses and lower-level groups. Taking all of this into account, we focused our search on the following subclass and groups: 'A61N' representing 'Electrotherapy, magnetotherapy, radiation therapy, ultrasound therapy'; 'A61B6' representing 'Apparatus for radiation diagnosis, e.g. combined with radiation therapy equipment'; 'A61B18' representing 'Surgical instruments, devices or methods for transferring non-mechanical forms of energy to or from the body'; 'A61B34' representing 'Computer-aided surgery; Manipulators or robots specially adapted for use in surgery.' The entire search query was:

(CL = ((focal OR ablati OR thermal OR cryo* OR 'focused ultrasound' OR photodynamic OR brachy*) AND (therapy OR treatment OR surgery) AND (cancer OR tumour OR neoplasm) AND (instrument OR instrumentation OR 'equipment design' OR 'machine design' OR apparatus OR needle OR probe)) OR TI = ((focal OR ablati* OR thermal OR cryo* OR 'focused ultrasound' OR photodynamic OR brachy*) AND (therapy OR treatment OR surgery) AND (cancer OR tumour OR neoplasm) AND (instrument OR instrumentation OR 'equipment design' OR 'machine design' OR apparatus OR needle OR probe)) OR AB = ((focal OR ablati* OR thermal OR cryo* OR 'focused ultrasound' OR photodynamic OR brachy*) AND (therapy OR treatment OR surgery) AND (cancer OR tumour OR neoplasm) AND (instrument OR instrumentation OR 'equipment design' OR 'machine design' OR apparatus OR needle OR probe))) (A61B6 OR A61B18 OR A61B34 OR A61N) country:WO before:publication:20210601 after:publication:20000101 language:ENGLISH.*

2.2. Eligibility criteria

The scope of this study was to make an overview of medical instruments that use focal therapy to treat localized cancer. Solely patents explaining the mechanical design of an *in vivo* focal therapy instrument to treat internal localized cancer were included. Patents for general focal therapy devices (i.e. not specifying the type of focal therapy, such as a single instrument that houses a catheter for cryotherapy, thermal treatment or delivery of a chemical agent or a single instrument designed to achieve ablation by microwave, radiofrequency, ultraviolet, ultrasound, or laser energy) and patents only focusing on the method of focal therapy but not on a device were excluded. Instruments only intended for veterinary medicine and instruments only for imaging, positioning, navigating, or monitoring were also excluded. Patents that only added a feature that does not relate to the focal working mechanism of an instrument presented in a different patent were excluded as well.

2.3. Patent search results

The search yielded 780 patents (last update 1 June 2021). Based on the eligibility criteria, the titles, and when in doubt, the abstracts, figures, and full-texts were checked subsequently. After full-text inspection, 128 patents were identified, fulfilling all eligibility criteria (Figure 1(b)).

2.4. Classification of focal therapy instruments

The results of our patent search revealed two types of targets of the focal therapy treatment: the individual cancer cells and the network of the cancer cells. In both cases, two types of

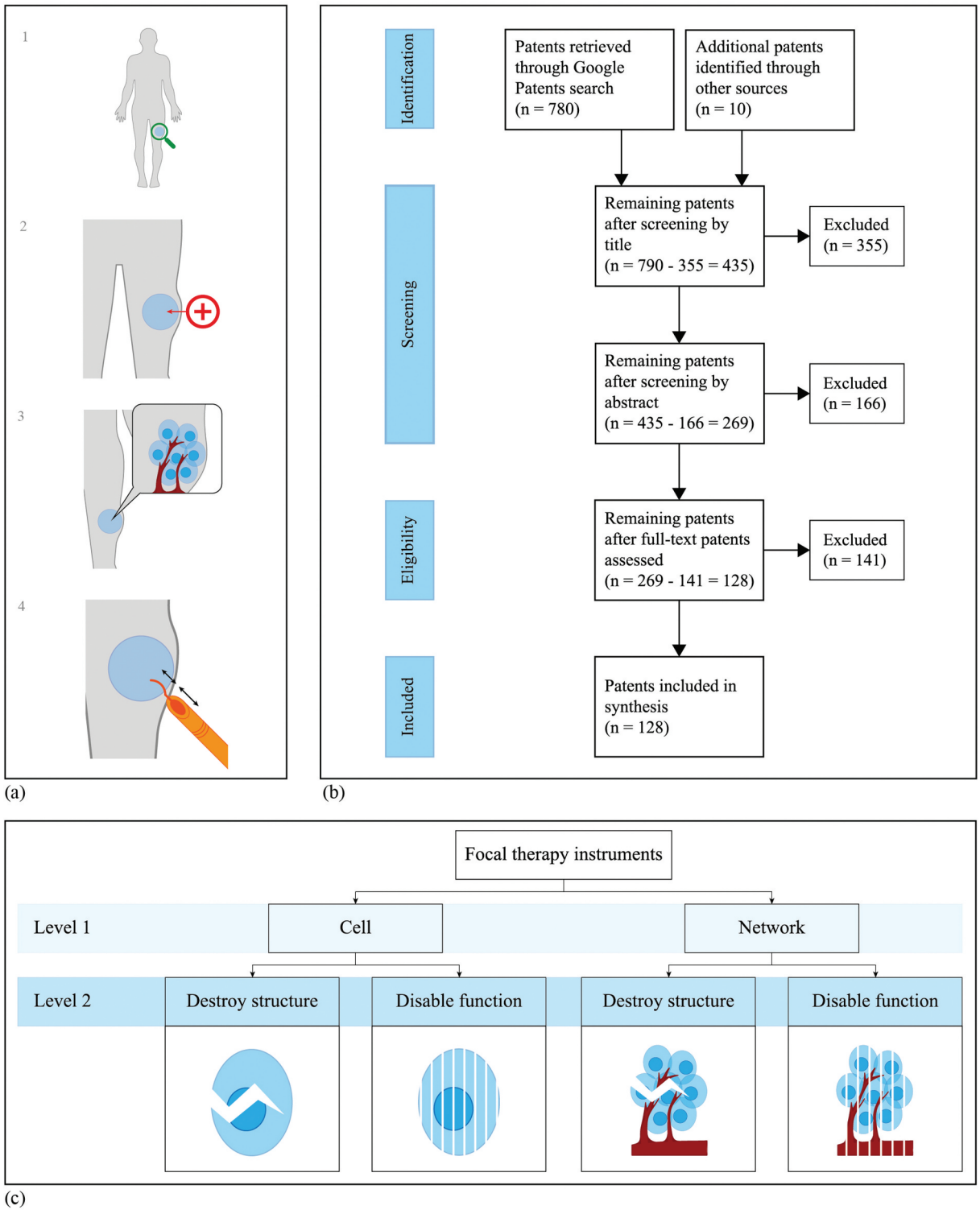


Figure 1. (a) Visual representation of the search query. (1) The first group of keywords limits the search to focal activities (rather than global/systemic). (2) The second group of keywords limits the search to treatments to cure the target area. (3) The third group of keywords limits the search to localized cancer. (4) The fourth group of keywords limits the search to the tool design. (b) Schematic representation of the patent selection method. (c) Focal therapy instruments are classified as either targeting the individual cancer cells or the network of cancer cells. In either case, two types of treatment purposes can be distinguished: to destroy the structure or to disable the function.

treatment purposes were identified: to destroy the structure or to disable the function (Figure 1(c)). For each of these purposes, we made a distinction between instruments that use energy (e.g. heat caused by electromagnetic waves, ultrasound waves, or thermally conductive elements) to interact with the individual cells or the network, instruments that use matter (e.g. chemical substances such as ethanol and antiandrogen), and instruments that use a combination of energy and matter (e.g. magnetic particles in combination with a magnetic field or photosensitive particles activated by light).

3. Destroy cancer cells on a cell level

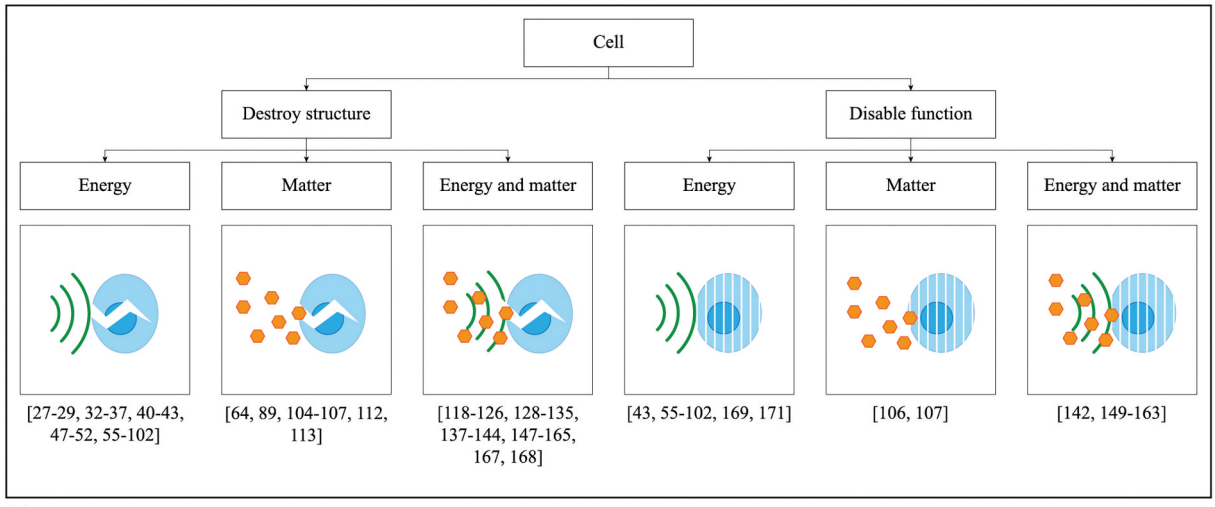
Focal therapy instruments that target the individual cancer cells apply their treatment on each cell, thereby destroying the structure (Section 3.1) or disabling the function (Section 3.2) of each cell. The classification of the patents on focal therapy instruments to treat cancer on the individual cancer cell level resulted in six groups of focal therapy instruments. Figure 2(a) presents a graphical summary of the instrument classification, listing all the retrieved patents for each group of focal therapy instruments. Each subsubsection describes the mechanical design variations of the focal therapy instruments classified into one group and the specific cancer types for which the instruments are designed.

3.1. Destroy cell structure

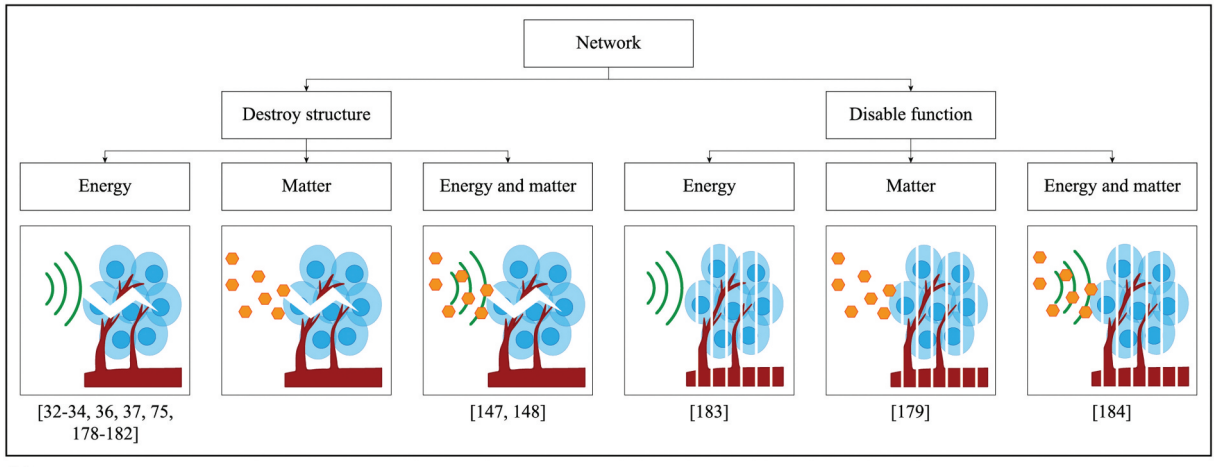
3.1.1. Destroy cell structure by applying energy

Sixty-seven patents were retrieved presenting instruments that destroy the structure of cancer cells by applying energy to the cells. A number of mechanical design variations, applying various types of energy, have been developed, targeting different parts of the cell structure. To date, most focal therapies using energy as a destruction mechanism are achieved by either high intensity focused ultrasound (HIFU) or cryotherapy [20–22]. Other focal therapies using energy to destroy the cell structure comprise irreversible electroporation (IRE), brachytherapy using ionizing radiation, and various treatment methods inducing thermal ablation or photodisruption [23].

Ultrasound is a form of mechanical wave transmission [24]. HIFU can be used for both thermal and mechanical destruction mechanisms [25]. Non-thermal ultrasound induces dense, energetic bubble clouds or boiling bubbles combined with shock fronts causing cell death by mechanical disintegration, called histotripsy [26]. Histotripsy is achieved using acoustic pulses with an intensity that is at least five times higher than the intensity of ultrasound used in thermal ablation [25]. As an example of non-thermal ultrasound, the instrument described by Roberts et al. [27] contains an external ultrasound transducer placed on a robotic arm to treat prostate tumors (Figure 3(a)). The ultrasound system is in acoustic contact with the patient's perineum. It controllably applies ultrasound energy into the prostate by maintaining a bubble cloud within the image generated by a transrectal ultrasound probe. A similar



(a)



(b)

Figure 2. (a) Classification of focal therapy instruments to destroy cancer cells on cell level. (b) Classification of focal therapy instruments to destroy cancer cells on network level.

external ultrasound transducer design was developed for brain cancer treatment [28]. A design for an internal probe that delivers pulsed electric energy for non-thermal cell destruction was described by Gleiman et al. [29].

Cryoablation relies on removing thermal energy from tissue to cause local freezing and consequently physical disruption due to mechanisms such as intracellular ice, ice crystals that cause shear stress, or extracellular ice crystals that remove water from cells [30]. The low temperature is achieved by the Joule-Thomson effect that describes the decrease in temperature of a fluid caused by the decrease in pressure on the fluid [31]. To illustrate, in the cryoprobe described by Surtees et al. [32] (Figure 3(b)), the tip of the cryoprobe is positioned adjacent to the target cells and is cooled by a cryogen gas to less than −50°C and subsequently heated to 5°C using both active and passive thawing in free-thaw-freeze cycles [5],

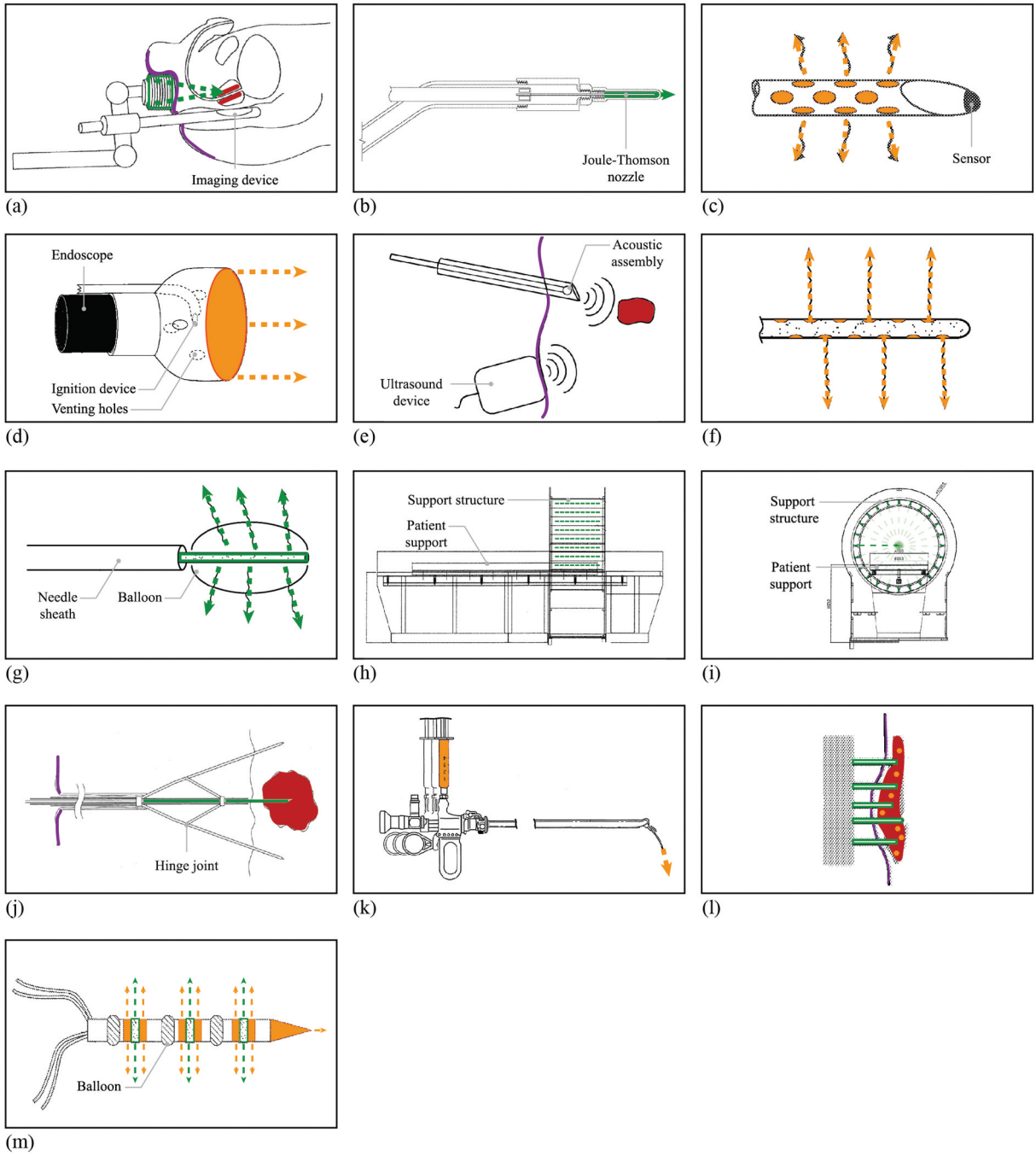


Figure 3. Patents of focal therapy instruments to destroy the cancer cell structure or disable the cancer cell structure. The drawings show the outline of skin the instrument encounters (purple), the energy transducing element (green), the energy sent to the target (green dashed), the matter source (orange), the matter sent (orange dashed), and the target region (red). (a) Instrument for nonthermal ultrasound treatment, from [27]. (b) Instrument for cryoablation, from [32]. (c) Distal tip of instrument for chemical ablation, from [104]. (d) Cap for cold plasma ablation, from [112]. (e) PDT instrument inserted in the patient showing the ultrasound monitoring system, from [118]. (f) Photosensitizer released from the perforations in the distal needle shaft, from [118]. (g) Needle sheath withdrawn exposes the fiber optic tip for light delivery, from [118]. (h) Instrument for magnetic treatment (front view), from [169]. (i) Instrument for magnetic treatment (side view), from [169]. (j) Instrument for thermal treatment using radio waves, from [58]. (k) Instrument for antiandrogen administration, from [107]. (l) Instrument using injectable MENPs and a magnetic field system, from [142]. (m) Instrument for thermal treatment using electrodes and dissolvable salts, from [152].

causing cell destruction. The cryogen gas is throttled through a Joule-Thomson nozzle and subsequently circulated within the probe. Heat is drawn from the target cells, and a growing ice mass is formed around the tip, eventually encompassing the target cells. The instrument further includes an ultrasound component for intra-procedural monitoring. Similar cryoprobes have been proposed by a number of inventors [33–35]. Other design variations include an instrument consisting of multiple rigid probes in a grid [36] or a flexible endoscopic catheter [37].

An electric field in contact with cells causes IRE by changing the electrochemical potential across the cell membrane, which opens the cell membrane causing the cells to die [38]. The irreversibility depends on the voltage, waveform, and frequency of the current [39]. IRE instruments designed to be introduced inside the body can consist of an implant [40] or a percutaneous handheld probe [41–43].

Electromagnetic radiation can be described as a wave or a collection of particles, known as photons [44]. We classified focal therapy instruments using electromagnetic radiation as instruments using energy instead of matter, because photons possess no rest mass. The electromagnetic spectrum can be divided into non-ionizing and ionizing radiation. The boundary between non-ionizing and ionizing radiation occurs in the ultraviolet field but is not strictly defined [45]. Ionizing radiation causes chemical bonds to break by removing electrons, whereas non-ionizing radiation only causes heating of the substance [45]. Ionizing radiation causes cell death by depositing energy in cancer cells, thereby damaging their genetic material [46]. Instruments have been developed using different types of ionizing radiation, including X-ray radiation [47–49], gamma-radiation [50], and light radiation [51,52].

Ablative technologies relying on high temperature (>60°C) affect both the cell structure and the cell function causing coagulative necrosis [39]. Coagulative necrosis is a form of necrosis where both the structural proteins and the enzymes of the cell are damaged, which partly explains the late onset of dead tissue removal in this type of necrosis [39,53]. Instruments can use different heat-generating or transmitting mechanisms to achieve cell death, including non-ionizing electromagnetic waves (i.e. radio waves, microwaves, and light), thermally conductive elements, and ultrasound waves. For electromagnetic waves, there is a trade-off between penetration depth and focusing [54]. Therefore, most instruments relying on electromagnetism are instruments in direct contact with the target tissue (e.g. internal probes or implants). This applies to radio wave probes [55–74], radio wave implants [75], microwave probes [76–84], and laser light probes [85,86]. Direct contact is also necessary for heat-conducting and electrification probes [43,87–89]. An exception is an external microwave system that uses two or more microwave transducers with reinforcing wave patterns to achieve the required penetration depth without direct contact with the target tissue [90]. Besides non-ionizing electromagnetic waves, ultrasound (e.g. HIFU) can also destroy and disable cancer cells [25]. Thermal HIFU does not cause mechanical disintegration of the cells like non-thermal HIFU, but it causes coagulative necrosis. HIFU can achieve adequate tissue penetration without affecting the focusing because it is a mechanical wave [54], which enables the design of external ultrasound transducers [91–96], as well as internal ultrasound probes [97–101] and implants [102] for thermal ultrasound.

Most patents focusing on destroying cancer cells based on energy principles describe instruments used for cancer treatment in general. However, some patents describe body-part specific cancer treatments, including brain cancer [28,102], lung cancer [61,66,74,90], breast cancer [93,96], endometrial cancer [67], adrenal cancer [64], prostate, thyroidal, bladder, or kidney cancer [27,47,50,51,94], and cancer in body tracts such as the gastrointestinal or urinary tract [47,52].

3.1.2. Destroy cell structure by applying matter

Eight patents were retrieved presenting instruments that destroy the structure of the cancer cell by applying matter to the cells. Focal therapy modalities using matter to destroy the cell structure are chemical ablation and cold atmospheric plasma (CAP).

Chemical ablation is the non-thermal, percutaneous ablation of target cells using ablative substances (e.g. ethanol) [103]. The ablative substance generally achieves cell destruction by dehydration of the cytoplasm, protein denaturation, and coagulation necrosis [103]. Toth et al. [104] describe a suitable probe for the internal delivery of a chemical agent (Figure 3(c)). The distal end of the probe is able to penetrate the target tissue and has delivery ports arranged along it. A balloon at the tip ensures contact between the target tissue and the delivery ports. Sensors at the tip allow for intra-procedural monitoring by measuring, temperature, physiological, and/or electrophysiological changes associated with the delivery process. Similar chemical delivery probes are presented in a number of other patents [64,89,105–107].

CAP is a treatment modality based on quasi-neutral ionized gas [108]. CAP creates reactive oxygen and nitrogen species (e.g. hydroxyl, hydrogen peroxide, and nitrogen dioxide), which selectively kill cancer cells, by amongst others DNA damage [109–111]. Barthel [112] describes plasma-producing caps that fit at the end of an endoscope (Figure 3(d)). The cap contains multiple plasma delivery ports and an ignition device to produce the ionized plasma. The endoscope camera can be used for intra-procedural monitoring. A similar design was presented by Krasik et al. [113].

Some patents for destroying cancer cell structures using matter have been developed for body-part-specific cancers, including esophageal cancer [112], adrenal cancer [64], and prostate cancer [105,107].

3.1.3. Destroy cell structure by applying energy and matter

Forty-six patents have been found presenting instruments that destroy the structure of the cancer cells by applying both energy and matter to them. Photodynamic therapy (PDT) is one of the best-studied focal therapy modalities for cancer treatment [114]. Other focal therapy modalities using combined energy and matter to destroy the cell structure are particle brachytherapy, reversible electroporation, and cryotherapy.

PDT involves administering a photosensitizer followed by activating the photosensitizer by the irradiation of a specific wavelength [115–117]. The activated photosensitizer generates radical oxygen species (superoxide and hydroxyl) that cause irreparable damage to the cell structure, thereby killing the cells [115]. Chen et al. [118] developed a needlelike probe comprising an internal passageway to introduce an acoustic assembly (Figure 3(e)), a photosensitizer assembly (Figure 3(f)), and a photoactivation assembly (Figure 3(g)). The probe can be positioned percutaneously or endoscopically and comprises a balloon to lock the device in place. An external steering mechanism is used to orient the distal end of the probe within the target region. The acoustic assembly in combination with the ultrasound device is used as an intra-procedural monitoring system. The photosensitizer is delivered from the perforations in the distal needle shaft of the photosensitizer assembly to the target cells adjacent to the outer surface of the target region. The photosensitizer is activated by an optical fiber delivered through the photoactivation assembly. Similar probe designs [119–122], or design variations with separate internal delivery instruments [123,124], or an internal and external delivery instrument [125,126] have also been reported.

Ionizing radiation with charged particles is able to cause DNA damage in the cancer cells [127]. In contrast to the ionizing radiation using photons described in Section 3.1.1, we classified ionizing radiation with charged particles as instruments that use matter because the charged particles do possess a mass. Patents were found using alpha-particles [128–131], beta-particles [131,132], neutrons [133], or positrons [134]. Most instruments have been developed to be placed internally (i.e. internal probes, needles, or implants) [128–132] because of the low penetration depth of particles, except for neutrons. High energy atoms, called plasma, do not target the cell DNA but aim at destroying the cell structure as a whole by thermal tissue evaporation, using an internal probe [135].

Reversible electroporation is able to cause cell death by increasing the membrane permeability to enable access to a cytotoxic agent (electrochemotherapy) [136]. The electrodes and the cytotoxic agent can be co-positioned [137,138] or introduced separately [139]. IRE can be enhanced by systemically administered nanoparticles that increase the treatment area or the cancer cell selectivity [140,141], magneto-electric nanoparticles responsive to magnetic fields [142], or a conductive fluid [143,144].

Cryotherapy instruments, as described in Section 3.1.1, are hindered by the risk of sticking to and tearing tissue, as well as their requirement for precise contact [145,146]. We found two patents describing a flexible catheter that delivers low-temperature matter (spray cryotherapy), to overcome these problems [147,148].

Some hyperthermia mechanisms to destroy cancer cells require a combination of energy and matter. A distinction can be made between a single medium that contains both the energy and the matter (e.g. a heated fluid or vapor delivered with an internal probe) [149,150] and different mediums for the energy and the matter. For the latter, a distinction can be made between a single instrument that administers both the energy and the matter (e.g. an internal probe with distinct channels) [151–156], separate instruments for the energy and the matter [157,158], and a single instrument that delivers either one of them (externally for ultrasound and magnetic systems and internally for electromagnetic wave systems) and a general instrument used in surgery to deliver the other (e.g. nanoparticles administered by injection, orally, or nasally) [159–165]. Another mechanism for focal treatment is local drug delivery using thermosensitive liposomes [166]. The internally administered liposomes can be activated by an internal probe [167] or an external system [168].

Most patents developed to destroy cancer cells based on combined energy and matter principles describe an instrument used for cancer treatment in general. However, some instruments for body-part-specific cancer treatment have also been reported, including brain cancer [143], lung cancer [148], cancer in the female reproductive system [147], and prostate cancer [150].

3.2. Disable cell function

3.2.1. Disable cell function by applying energy

Fifty-one patents were retrieved presenting instruments that disable the function of the cancer cells by applying energy to the cells. Both magnetism and hyperthermia can be used to disable the cell function.

In Vishwanath [169], an external magnetic system for cell degeneration was described. Cell degeneration is achieved by normalizing the cell membrane potential, causing an increased influx of calcium and potassium ions and oxygen, an increased efflux of sodium and water, and a reduction of the intracellular acidity. Only cancer cells are affected because of their low membrane potential as compared to healthy cells [170]. The system described by Vishwanath [169] consists of multiple magnetic field generators circumferentially fixed on a support structure (Figure 3(h) and 3(i)). The system is placed externally from the patient in such a way that the target cells are at the focal region of magnetic field generators. Monitoring of the treatment can be done using pre- and post-treatment imaging modalities, such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Another design variation of an instrument that changes the cell membrane potential is a probe with contact electrodes [171].

Other instruments use hyperthermia mechanisms, which damage the cell directly (see Section 3.1.1), but also disable the cell function [39]. Habib [58] developed a set of radiowave emitting needles that can be deployed by a hinge joint at the central needle (Figure 3(j)). The radiofrequency power can be applied across different combinations of the needles. The instrument can be used in conjunction with an imaging system, such as ultrasound, for intra-procedural monitoring. Some examples of cell functions that are disabled are the process of facilitated diffusion across the cell membrane with the assistance of membrane proteins and the mitochondrial function [172,173]. Other instruments that apply hyperthermia mechanisms using energy to disable the cell function have been found in a number of patents [43,55–102].

Most patents developed to disable cancer cells based on energy principles describe an instrument used for cancer treatment in general. However, some instruments for body-part specific cancer treatment are reported as well, including brain cancer [28,102], lung cancer [61,66,74,90], breast cancer [93,96], endometrial cancer [67], adrenal cancer [64], and prostate, thyroidal, bladder, or kidney cancer [94].

3.2.2. Disable cell function by applying matter

Using matter to disable the function of cancer cells targets (the production of) essential elements for the proliferation of the cancer cells with hormones or other agents. Only two patents have been found presenting instruments that target these essential elements using matter.

Neisz et al. [107] describe a probe for administering an antiandrogen that suppresses the androgen production by the testes (Figure 3(k)), for example, bicalutamide [174]. For androgen-dependent prostate cancer, androgen (typically testosterone) is required for the development of the tumor [175]. The transurethral probe contains a needle designed to be deployed against the prostate urethra. The probe includes a scope sheath with an eye-port for intra-procedural visual guidance. A similar design was presented by Barnett et al. [106] that can deliver various types of agents to block the production of essential elements for the cancer cells. Some possible agents are bicalutamide for prostate cancer cells and tamoxifen for breast cancer cells [176]. Tamoxifen inhibits estrogen binding to estrogen receptors, a binding required for tumor growth of the breast cancer cells [176].

3.2.3. Disable cell function by applying energy and matter

Sixteen patents were retrieved presenting instruments that disable the function of the cancer cells by applying both energy and matter to the cells. Both magneto-electric nanoparticles and particles enhancing hyperthermia mechanisms disable the cancer cell function in combination with applied energy.

Liang [142] developed injectable magneto-electric nanoparticles (MENPs) (Figure 3(l)). The MENPs are attracted to cancer cells because of the different electrical potentials of cancer cells and healthy cells. An external magnetic system induces three magnetic fields: the first magnetic field produces a higher concentration of MENPs at the tumor site, the second achieves nano-electroporation to penetrate targeted cells, and the third both disables the function of the target cells and physically damages the cells by mechanical motion of the MENPs inside the cell. Adding an MRI device may enable intra-procedural monitoring.

Other patents in this group use hyperthermia mechanisms to both destroy the cells and disable the cell function. Ruse et al. [152] presented an instrument consisting of multiple rigid electrode shafts with dissolvable salts (Figure 3(m)). The dissolvable salts mix with bodily fluids, resulting in an electrically conductive ionic solution. Inflatable components along the shafts provide mechanical stability. Each electrode shaft has a thermal sensor for intra-procedural temperature monitoring. Furthermore, the electrode bands and the non-conductive shaft portions can be distinguished using ultrasound imaging. Other instruments using hyperthermia mechanisms to disable the cell function using both energy and matter have been found in a number of patents [149–163].

Most patents that propose to disable cancer cells based on combined energy and matter principles describe an instrument used for cancer treatment in general, except for one patent developed for prostate cancer treatment [150]. Almost all instruments classified as disabling the individual cell function (Groups 4, 5, and 6) were also classified as destroying the individual cell structure (Groups 1, 2, and 3). These instruments apply a hybrid method that affects both the cell structure and the cell function to achieve cell death. The most frequently applied hybrid methods in instruments that target individual cancer cells are high-temperature ablative technologies using solely energy or combined energy and matter. All patents classified as disabling the cancer cell function apply a hybrid method that combines destruction and disabling mechanisms, except for a patent by Vishwanath [169] and a patent by Sano et al. [171] describing focal therapy instruments that focus solely on disabling the cancer cell function.

4. Destroy cancer cells on a network level

Focal therapy instruments targeting the network of cancer cells apply their treatment not on each cell but treat a network of cells as a whole. The cell network is able to live because of the supply of nutrients and the discharge of waste, enabled by the vascular system of the network. This function is disabled when the blood vessels and lymphatic vessels leading toward and from the cancer cells are either destructed (Section 4.1) or obstructed (i.e. disabled, Section 4.2) [177]. Both the destruction and obstruction of the pathways leading toward and from the cancer cells can be achieved by energy, matter, or a combination of energy and matter. The classification of the patents on focal therapy instruments to treat cancer on the network level resulted in six groups of focal therapy instruments (Figure 2(b)). Each subsubsection describes the mechanical design variations of the focal therapy instruments classified into one group and the specific cancer type for which the instruments are designed.

4.1. Destroy network structure

4.1.1. Destroy network structure by applying *energy*

Eleven patents have been found presenting instruments that destroy the structure of a cancer cell network by applying energy to the network as a whole (Figure 2(b)). The vascular system of the cancer cells can be destroyed with energy by either targeting the individual blood vessels or targeting the overall blood supply.

Habib [178] describes a flexible catheter containing multiple electrodes for thermal ablation of a blood vessel supplying a tumor using radiofrequency current (Figure 4(a)). The catheter is mounted on a guidewire, and the distal tip comprises extendable elements that can be deployed outwards from the shaft to contact the hollow vessel wall. Temperature sensors at the catheter tip allow for intra-procedural monitoring. Similar patents on instruments applying a heated lumen around the vessel [179] or inserting a catheter with a thermal probe inside a vessel [180] have been found. Another design variation comprises an ablating implant inserted in the blood vessel

[75,181]. Besides thermal ablation, cryoablation is also able to cause vascular injury (as well as direct cell destruction, making cryoablation a hybrid method, see Section 3.1.1), leading to cell death [5]. A number of instruments have been proposed that induce cryoablation of blood vessels by removing thermal energy [32–34,36,37].

Instead of targeting the individual blood vessels, another design variation targets the overall blood supply of cancer cells by embolizing a shell of tissue surrounding a group of cancer cells, thereby enclosing the cancer cells. Parsons et al. [182] describe an instrument that applies HIFU to the perimeter of the tumor, thereby both interrupting the blood supply of the cells in the interior region and treating the interior region by indirect heating (Figure 4(b)). The focal zone of the HIFU instrument is moved along the perimeter of the target volume. The time required to treat the target tissue is reduced as compared to treatment of the target tissue by direct ablation. The instruments includes an ultrasound imaging transducer for intra-procedural monitoring.

Most patents focusing on disabling cancer networks based on energy principles describe an instrument used for cancer treatment in general, except for a patent developed for lung cancer [180] and a patent developed for endometrial cancer treatment [182].

4.1.2. Destroy network structure by applying energy and matter

Two patents were retrieved describing instruments that destroy the cell network by applying energy and matter to the network. Cryoablation using low-temperature matter causes vascular injury (as well as direct cell destruction, see Section 3.1.3), leading to cell death [5]. Krimsky [147] describes a catheter coupled to a cryogen source that is inserted through a lumen of an endoscope into the patient's vagina or cervix to treat cancer in the female reproductive system. The catheter contains one or more openings for the cryogen that is sprayed directly on the target tissue (Figure 4(c)). The endoscope can additionally house an imaging camera lens for intra-procedural monitoring. Johnston [148] described a similar cryoablation instrument for lung cancer treatment.

4.2. Disable network function

4.2.1. Disable network function by applying energy

Only one patent has been found describing an instrument that disables the cell network by applying energy. Specifically, Connors et al. [183] describe an inflatable implant to be placed around a network of cancer cells (Figure 4(d)). This implant consists of a flexible housing filled with a high vapor pressure medium that forms a shell around the cancer cells. The inner surface of the implant inflates over time, thereby constricting the cells and the blood flow to the cells by the applied pressure. The instrument has been developed to treat problems with pressure in the body, such as urinary incontinence, and to treat cancer cell networks. The implant can optionally include an electronic device to monitor and control the expansion and contraction intra-procedurally.

4.2.2. Disable network function by applying matter

Gat et al. [179] describe an instrument that disables the network function by applying matter. The instrument was developed to treat testosterone-dependent prostate cancer using an intravascular catheter. The catheter is capable of sclerosing an internal spermatic vein (the deferential vein), thereby preventing blood rich in testosterone from reaching the prostate (Figure 4(e)). A guidewire within the catheter enables the

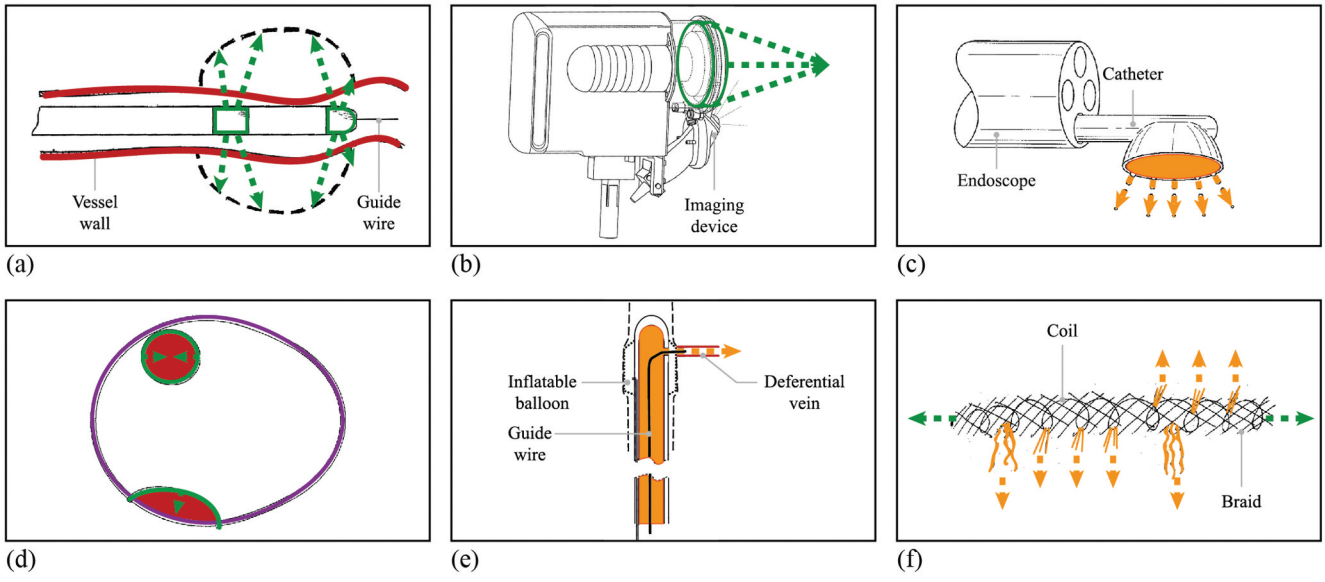


Figure 4. Patents of focal therapy instruments to destroy the cancer cell network structure. The drawings show the outline of skin the instrument encounters (purple), the energy transducing element (green), the energy sent to the target (green dashed), the matter source (orange), the matter sent (orange dashed), and the target region (red). (a) Instrument using electrodes to embolize a vessel leading to cancer cells, from [178]. (b) Instrument using flexible electrodes to embolize a shell of tissue surrounding a network of cancer cells, from [182]. (c) Instrument using cryoablation to cause vascular damage, from [147]. (d) Instrument to constrict cancer cells and its blood flow, from [183]. (e) Instrument to deliver sclerosing agent to the deferential vein to prevent testosterone from reaching the prostate, from [179]. (f) Instrument using pressure and an anti-cancer factor to block a vessel leading to cancer cells, from [184].

positioning of the catheter's orifice in front of the target junction and an inflatable balloon to hold the catheter in place and prevent the agent from reaching other regions than the target region. Intra-procedural imaging using optical fibers, ultrasound, or CT allows for positioning of the catheter. The catheter then injects a sclerosing agent into the opening of the target vein, which causes swelling that cuts off the blood flow, after which the vein shrinks. Optionally, an anti-androgen is injected after occluding.

4.2.3. Disable network function by applying energy and matter

Only one patent [184] has been retrieved that describes an instrument that disables the cancer network function by applying energy and matter. The patent describes an implant that obstructs blood vessels while emitting a bioactive agent, such as an anti-cancer factor (Figure 4 (f)). The instrument comprises a helical coil designed to be deployed inside the patient's blood vessel. A braid positioned over the helical coil like a sleeve contains fibrous elements comprising the bioactive material. Plugs, attacked to the braid, obstruct the target vessel. External imaging modalities can be used to monitor the positioning of the implant. The instrument was designed to obstruct abnormal blood flow sites, such as blood vessels that carry blood to cancer cell networks.

5. Commercially available instruments

This section provides a glimpse of the current commercially available focal therapy instruments to treat localized cancer. Most commercially available instruments destroy the cancer cell structure by applying energy (Group 1), such as cryotherapy and hyperthermia treatments, which are hybrid treatments that also affect the cell function (Group 4), or by applying combined energy and matter (Group 3) such as PDT and electrochemotherapy (Table 1). The patents related to the commercially available instruments were collected by analyzing to which company the patent was assigned and evaluating the resemblances between the patented instrument and the commercially available instrument.

Common cryotherapy probes are the IceSeed™ MRI or IceRod™ MRI (Boston Scientific, Natick, MA) [185] used with the Visual-ICE Cryoablation system [186]. A patent of these probes was presented by Zvuloni et al. [36]. Another commercially available cryoprobe is distributed by Endocare (Healthtronics/Endocare Inc., Irvine, CA), which is used under ultrasound guidance [187]. All three cryoprobes create an ice ball formation at the tip by compressed argon gas that passes through a central channel [188].

IRE has been approved in Europe (CE certificate), as well as by the FDA in the US [189]. The NanoKnife (AngioDynamics, Queensbury, NY) [190,191] is the first instrument based on IRE [192]. Two patents on instruments discussed in this study are assigned to AngioDynamics and are related to the NanoKnife as they show similar treatment mechanisms [42,43]. The NanoKnife consists of a set of monopolar probes and one bipolar probe that are positioned with ultrasound or CT guidance [193].

Common thermal mechanisms that disable cell function and destroy cell structure are radiofrequency ablation (RFA), microwave ablation, HIFU, and focal laser ablation. Multiple companies manufacture RFA instruments, which are used under ultrasound or CT guidance. Boston Scientific (Natick, MA) distributes the LeVeen Needle Electrode [194], consisting of twelve curved electrodes that open in an umbrella shape. Three found patents on RFA probes are assigned to Boston Scientific and show a similar umbrella shape and treatment mechanism as the LeVeen Needle Electrode [60,70,71]. Covidien (Mansfield, MA) distributes the Cool-tip RFA System [195], in which the probe contains either a single electrode or a set of up to three electrodes. AngioDynamics (Queensbury, NY) developed a number of RFA devices, including the StarBurst XL and the StarBurst Semi-Flex [196], the latter being able to bend up to 90 degrees in all directions. The

Table 1. Overview of commercially available focal therapy instruments to treat localized cancer.

Instrument	Company	Reference	Related Patent(s)	Classification Group(s)	Focal Therapy Method
IceSeed™ MRI	Boston Scientific, Natick, MA [185]	[169]	[36]	1. Destroy cell structure by applying energy	Cryotherapy
IceRod™ MRI	Boston Scientific, Natick, MA	[185]	[36]		
Endocare™ precision cryoprobe	Healthtronics/Endocare Inc., Irvine, CA	[186]			
NanoKnife	AngioDynamics, Queensbury, NY	[187,188]	[42,43]		IRE
LeVeen Needle Electrode	Boston Scientific, Natick, MA	[189]	[60,70,71]	1. Destroy cell structure by applying energy and4. Disable cell function by applying energy	RFA
Cool-tip RFA System	Covidien, Mansfield, MA	[190]			
Starburst XL	AngioDynamics, Queensbury, NY	[191]			
Starburst Semi-Flex	AngioDynamics, Queensbury, NY	[191]			
Solero Microwave Tissue Ablation System	AngioDynamics, Queensbury, NY	[192]			Microwave ablation
TULSA-PRO	Profound Medical Inc., Toronto, Canada	[193]			HIFU
Sonalleve MR-HIFU	Profound Medical Inc., Toronto, Canada and Philips Healthcare, Best, The Netherlands	[194,195]	[91,96]		
Focal One HIFU device	EDAP TMS, Vaulx-en-Velin, France	[196]			
Ablatherm Robotic HIFU device	EDAP TMS, Vaulx-en-Velin, France	[197]			
Sonablate	SonaCare Medical, Charlotte, NC	[198]			
Foscan or padeliporfin (TOOKAD) and a laser diode	Applied Optronics Corp., South Plainfield, NJ	[199–201]		3. Destroy cell structure by applying energy and matter	PDT
Cliniporator 2	IGEA, Carpi, Italy	[202]			Electrochemo-therapy

IRE = irreversible electroporation; RFA = radiofrequency ablation; HIFU = high intensity focused ultrasound; PDT = photodynamic therapy

probe contains nine deployable electrodes and an active trocar tip. AngioDynamics also distributes the Solero Microwave Tissue Ablation System, which contains an internal thermocouple for intra-procedural monitoring [197]. These commercially available RFA and microwave ablation instruments are instruments for cancer treatment in general based on coagulative necrosis. A transurethral HIFU system for prostate cancer treatment under MRI-guidance is distributed by Profound Medical Inc. (Toronto, Canada) and called the TULSA-PRO [198]. They also distributed the Sonalleve MR-HIFU system (in cooperation with Philips Healthcare (Best, The Netherlands)) [199,200] for breast cancer treatment under MRI-guidance. Two patents on external HIFU systems discussed in this study are assigned to Philips Healthcare and show a similar treatment mechanism as the Sonalleve MR-HIFU system [91,96]. Commercially available HIFU instruments for transrectal prostate cancer treatment under ultrasound-guidance are the Focal One HIFU device, the Ablatherm Robotic HIFU device (EDAP TMS, Vaulx-en-Velin, France), and the Sonablate (SonaCare Medical, Charlotte, NC) [201–203].

PDT in common clinical practice consists of an injection of a photosensitizer, such as Foscan or padeliporfin (TOOKAD) [204,205], and the internal or external application of red light. A diode laser (Applied Optronics Corp., South Plainfield, NJ) [206] can be used to deliver light fibers to the internal cancer site [204]. For reversible electroporation used in electrochemotherapy to eventually cause irreversible damage, the Cliniporator 2 (IGEA, Carpi, Italy) [207] is in clinical practice in more than 100 clinical centers of the European Union [208]. Measurements of the voltage and current supplied allows for intra-procedural monitoring. For more information about commercially available tumor ablation instruments, we refer the reader to [3,19,209].

6. Discussion

This study aimed to provide a comprehensive overview of the patent literature on focal therapy instruments to treat localized cancer. Twelve groups of treatment types performed by the focal therapy instruments were identified based on the treatment target, purpose, and means. A total of 18.0% of the relevant patents has been published and filed by independent inventors, 69.5% by companies, and 12.5% by academic institutions, indicating that, although both companies and academic institutions show interest in focal therapy instruments to treat cancer, the field is mostly industry-driven.

Once looking at the temporal distribution of the classification of the patents in Figure 5, it becomes apparent that certain focal treatment types are more frequently applied for than others. These treatment types target the individual cancer cells with solely energy or combined with matter (Groups 1, 3, and 4). This trend is consistent with the instrument types that are commercially available (see Section 5).

Regarding the treatment target, most patents describe an instrument targeted at the individual cancer cell rather than at the cancer cell network. Cancer cells can be seen as the direct target of cancer treatment, whereas blood vessels are an indirect target to treat those cancer cells. The blood vessels of cancer networks are poorly organized, which impairs particle delivery as cancer treatment [210,211]. Therapies targeting the blood vessels of cancer networks are relatively new and have only moved from the laboratory to the clinic since 1992 [212].

Considering the treatment purpose, a high number of patents describe an instrument that destroys a structure as compared to an instrument that disables a function. One could speculate that the preference for focal cancer treatment types that destroy a structure is due to their general

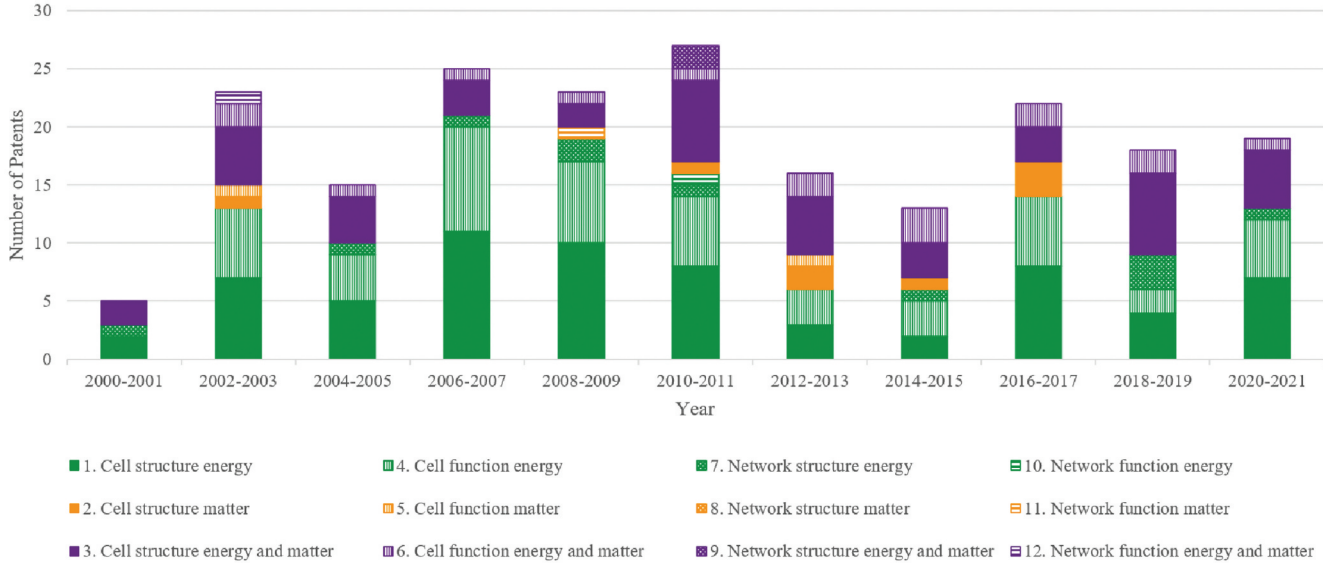


Figure 5. Temporal distribution of relevant patents published, classified on the instrument's treatment target (cell or network of cells), purpose (destroy the structure or disable the function), and means (energy, matter, and combined energy and matter). The patents retrieved were published between January 2000 and June 2021.

destruction mechanism. A structure is concrete and can be examined, in other words: a structure provides a static image, whereas a function is intangible and explainable only in terms of its underlying structures. This explains why there is less information about the functional changes due to cancer, in contrast to the structural/anatomic changes [213]. To disrupt the cancer cell or network function, information is required about the vital function and how to disrupt it, which requires imaging of the cell's dynamic workings. For the dynamic workings, often only indirect monitoring methods exist, making the area of physiological modeling less intuitive than anatomical modeling [214]. A general destruction mechanism might therefore be easy to design as compared to a function disabling mechanism. MRI, often used for monitoring, has only recently evolved from being purely anatomy-based to a discipline that is able to incorporate both anatomic and physiologic information with the addition of functional MRI [215–217].

With regard to the treatment means, most patents describe an instrument using energy. The low preference in using matter to treat cancer might be explained by the long-term toxicity concerns of remaining matter, especially non-biodegradable matter [218,219]. Energy does not possess this risk of long-term toxicity, as the energy is removed from the body together with the removal of the energy source. Another barrier of matter is the body's labeling of foreign particles by opsonization to stimulate the removal of those foreign particles [218]. In opsonization, the foreign particles are covered with nonspecific proteins to make them more visible to phagocytic cells, so phagocytosis can occur [218,220].

Figure 5 shows that there is no specific trend toward the design of an instrument that accomplishes a certain type of treatment. The temporal distribution of the patents in the field of focal therapy instruments shows a persisting number of patents being published with an increase from 2016 on. Focal therapy rapidly advanced in the 1990s, as cross-sectional imaging became commercially available and widespread [39,103]. Focal therapy first gained clinical acceptance as a method for treating cancer in the liver, kidney, lung, and bone [103]. In 2016, a randomized controlled trial was conducted to evaluate the outcomes of the three contemporary treatment modalities of localized prostate cancer (i.e. active monitoring, surgical resection, and radiotherapy), called the ProtecT trial. After a median follow-up of 10 years of 1643 randomized participants, Hamdy et al. [18] demonstrated no significant difference in prostate-cancer-specific mortality. Nevertheless, the rates of disease progression and rates of metastases development were higher for active monitoring than for surgery and radiotherapy [18]. This outcome increased the interest in less radical treatments, such as focal therapy, for localized prostate cancer [221]. An explanation of the increasing number of published patents from 2016 onwards could be the outcomes of studies such as the ProtecT trial and the increased rate of early diagnosis of prostate cancer [222], the latter increases the chances for positive outcomes of focal therapy, as the cancer is still locally confined [5]. Patients with organ-confined cancer were considered suitable candidates for focal therapy in multiple consensus projects on focal therapy as prostate cancer treatment [223].

Furthermore, Figure 5 shows that patents published on focal therapy instruments that destroy or disable the individual cancer cell using energy (Groups 1 and 4) and destroy the individual cell using combined energy and matter (Group 3) remain dominant throughout the years. Nevertheless, there is a trend toward an equal distribution of the different groups applied for in patented focal therapy instruments, leading to a more varied spectrum of focal therapy instruments in the patent literature. Instruments destroying cell structure using matter (Group 2), disabling cell function using energy and matter (Group 6), and destroying network structure using energy (Group 7) gain their share in the focal therapy field besides the dominant focal treatment types (Groups 1, 3, and 4). Patents on instruments that disable a network function (Groups 10, 11, and 12) filed until 2011 can be seen in Figure 5, indicating that inventors touched upon these treatment types. However, these treatment types were no longer applied for in the patent literature of the last eight years. This smothering effect might indicate that disabling the network function is medically not feasible. Disabling of a cancer network by obstructing the blood vessels results in metabolic stress, which might turn on the 'angiogenic switch' [224], increasing the tumor angiogenesis to compensate for the obstructed blood vessels. Patents on instruments that disable cell function using matter (Group 5) and instruments that destroy network structure using energy and matter (Group 9) are also not applied for anymore.

The observation that instruments for destroying or disabling the individual cancer cell using energy (Groups 1 and 4) show similar changes in the number of patents throughout the years can be explained by instruments that apply hybrid methods. Almost all patents classified as disabling the individual cell function (Groups 4, 5, and 6) are also classified as destroying the individual cell structure (Groups 1, 2, and 3), performing hybrid methods. This means that there are barely any patents describing focal therapy instruments that focus solely on disabling the cancer cell function. The group of patents that perform a hybrid method mainly consist of instruments that rely on high-temperature ablative technologies that affect both the cell structure and the cell function causing coagulative necrosis [39].

7. Conclusion

This review article provides a comprehensive overview and classification of the patent literature on focal therapy instruments to treat localized cancer. We analyzed the different mechanical designs present in the instrument patents. The medical section of the Google Patents database was reviewed, and 128 patents published in the last two decades (2000–2021) were discussed.

We proposed a classification of the possible treatment types applied by instruments for focal therapy based on the target, purpose, and means of treatment. At the fundamental level, the individual cancer cells and the network of cancer cells were distinguished as targets. The working mechanism can be based on destroying the structure or disabling the function. Based on the means of establishing this treatment

mechanism, the means can be distinguished as energy, matter, or combined energy and matter.

The most preferred treatments applied by the instruments were identified as to destroy the cell structure using solely energy or combined energy and matter, or to disable the cell structure using energy. The description of the different instrument functions may serve as a source of inspiration for new focal therapy instruments to treat localized cancer.

8. Expert opinion

8.1. Design suitability for medical purposes

In this review, the mechanical design principles were analyzed by looking at patented working principles without considering the technical and medical feasibility of these principles, which usually cannot be found in patent literature. The main risks of choosing focal therapy are the multifocality of cancer and the risk of undetectable micro-metastases [3,225]. Adequate patient selection is therefore of utmost importance. Multifocality implies the presence of two or more tumor foci (microscopically visible group of cells) separated by healthy tissue, whereas unifocal means that only one tumor focus is observed [226,227]. Multifocal cancer treated with focal therapy might result in incomplete treatment because of missed foci, leading to cancer recurrence [228,229].

Another hurdle lies in the efficacy of the indirect cancer cell treatment by targeting its vascular network. Tumor growth and metastatic spread of cancer tissue require the formation of a new vascular network called angiogenesis, consisting of blood vessels and lymphatic vessels [12,211]. Therapies targeting the formation of the cancer network using systemic antiangiogenic drugs only yielded modest responses and no long-term survival benefits [230]. These results were explained by resistance mechanisms of the cancer cells (evasive resistance) that cause revascularization [231]. Therefore, the efficacy of the instruments described in the patents targeting the network of cancer cells is questionable considering these resistance mechanisms. Vascular targeted therapies might result in such an elaborate vaporization of vessels that the tumor is unable to neovascularize. However, when the vaporization is not elaborate enough, instruments that destroy or disable the vascular system of the cancer cells might encounter similar resistance strategies of the cancer cells.

Considering implants that require placement around the network of cancer cells, such as the inflatable implant presented in a patent by Connors et al. [183] (see Section 4.2.1), we question the medical feasibility concerning the dissemination of tissue at the trajectory of implant placement. The implant is designed to be positioned around a network of cancer cells. However, the separation of the network of cancer cells from the surrounding cells to enable the implant placement might lead to disseminating malignant tissue in the body.

8.2. Further research

This review focuses on the mechanical design of focal therapy instruments applying different treatment types. The search was restricted to focal therapy instruments to treat cancer, thereby leaving out focal therapy instruments originally designed for the treatment of other medical causes. As focal therapy is not only of interest for cancer treatment but also for the treatment of for example, abnormal blood flow in the heart, the results from other medical technology fields could lead to other creative solutions for cancer treatment. The definition used for focal therapy in this review excludes instruments developed for resecting cancer cells. An example of such an instrument is an instrument that focally ablates cancer cells prior to the resection to prevent bleeding during the resection. The field of instrumentations that use focal therapy prior to resection might illustrate new treatment types that could be applied to focal therapy instruments that do not apply this subsequent resection.

This review considers patents to provide a comprehensive overview of the patent literature on focal therapy instruments to treat localized cancer. For further research, it is of interest to explore the corresponding scientific literature as well as to analyze the performance of the instruments described in the patents. For focal therapy to be viable, accurate imaging is required for proper diagnosis of cancer localization and to accurately reach the location of the cancer cells with the instrument [232]. Conventional imaging modalities comprise CT, ultrasound, and MRI, from which MRI enables the highest accuracy [232]. For MRI-guided focal therapy, the focal therapy instrument must be developed with special precautions regarding MRI compatibility [233]. For further research, it is important to integrate instrument development with the used imaging modality and its imposed requirements for the instrument, e.g. no metallic, ferromagnetic, and conductive materials for MRI compatible instruments [234].

The IDEAL framework for surgical innovation (idea, development, exploration, assessment, and long term study) allows for an estimation of the clinical development phase of the medical instruments [235]. For future research, a contemplation of the selected patents against the IDEAL framework could be an interesting addition to this study.

8.3. Five-year view

The trend toward an equal distribution of the different groups of patented focal therapy instruments results in a wider range of possible focal therapy instruments to treat cancer. The commercial availability and the clinical use are the results of different steps in the design process. We expect that the trend of a wider range of patents on focal therapy instruments will extend to the instruments tested on their medical feasibility. These upcoming focal therapy instruments might broaden the existing spectrum of commercially available instruments that use energy to destroy and disable the cancer cell structure and function, respectively (Groups 1 and 4), and instruments that destroy the cancer cell structure using combined energy and matter (Group 3). Focal therapy instruments focused on destroying the cancer cell structure using matter (Group 2), disabling the cancer cell function using both energy and matter (Group 6), and destroying the network structure using energy (Group 7) can be seen as a new generation of focal therapy instruments to treat cancer.

As far as new focal cancer cell treatment mechanisms are concerned, we identified one unexplored, yet theoretically

feasible treatment mechanism: to destroy the network structure using matter (Group 8). Instruments in this group would locally apply particles that destroy the vascular system of the cancer cells. The particles would function without the application of energy, and they would target the vascular system without directly affecting the individual cancer cells. The medical and mechanical feasibility of this treatment mechanism for cancer remains to be investigated.

Abbreviations

CAP, Cold atmospheric plasma; CT, Computed tomography; HIFU, High intensity focused ultrasound; IRE, Irreversible electroporation; MENP, Magneto-electric nanoparticle; MRI, Magnetic resonance imaging; PDT, Photodynamic therapy; RFA, Radiofrequency ablation.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

One peer reviewer is an employee of Avenda Health. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Funding

This paper was not funded.

ORCID

Jette Bloemberg http://orcid.org/0000-0002-6627-4165
Luigi Van Riel http://orcid.org/0000-0001-5759-3909
Dimitra Dodou http://orcid.org/0000-0002-9428-3261
Paul Breedveld http://orcid.org/0000-0002-7235-1657

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. CA Cancer J Clin. 2019 Jun.;69(5):363–385.
2. Beets GL, Figueiredo NF, Beets-Tan RG. Management of rectal cancer without radical resection. Annu Rev Med. 2017 Jan.;68:169–182.
3. Eggener SE, Scardino PT, Carroll PR, et al. Focal therapy for localized prostate cancer: a critical appraisal of rationale and modalities. J Urol. 2007 Dec.;178(6):2260–2267.
4. Ahmed HU, Pendse D, Illing R, et al. Will focal therapy become a standard of care for men with localized prostate cancer? Nature Clin Pract Oncol. 2007 Nov.;4(11):632–642.
5. Lodeizen O, De Bruin M, Eggener S, et al. Ablation energies for focal treatment of prostate cancer. World J Urol. 2019 Mar.;37(3):409–418.
6. Donaldson IA, Alonzi R, Barratt D, et al. Focal therapy: patients, interventions, and outcomes—a report from a consensus meeting. Eur Urol. 2015 Apr.;67(4):771–777.
7. Wu F, Zhou L, Chen WR. Host antitumour immune responses to HIFU ablation. Int J Hyperthermia. 2007 Jan.;23(2):165–171.
8. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011 Jan.;59(1):61–71.
9. Kutikov A, Kunkle DA, Uzzo RG. Focal therapy for kidney cancer: a systematic review. Curr Opin Urol. 2009 Mar.;19(2):148–153.
10. Wu F, Wang ZB, Cao YD, et al. "Wide local ablation" of localized breast cancer using high intensity focused ultrasound. J Surg Oncol. 2007;96(2):130–136.
11. Marieb EN, Hoehn K. Human anatomy & physiology. Tenth edition. London: Pearson education; 2016.
12. Nishida N, Yano H, Nishida T, et al. Angiogenesis in cancer. Vasc Health Risk Manag. 2006;Sep.;2(3):213-219.
13. Hsieh W-S, Simons JW. Systemic therapy of prostate cancer. New concepts from prostate cancer tumor biology. Cancer Treat Rev. 1993 Jul.;19(3):229–260.
14. Fischer JJ, Papac RJ. Theoretical considerations in combinations of localized and systemic therapy for neoplastic disease. J Theor Biol. 1972 Oct.;37(1):105–114.
15. Walsh PC. Radical prostatectomy for localized prostate cancer provides durable cancer control with excellent quality of life: a structured debate. J Urol. 2000 Jun.;163(6):1802–1807.
16. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med. 2008 Mar.;358(12):1250–1261.
17. Potosky AL, Davis WW, Hoffman RM, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst. 2004;96(18):1358–1367.
18. Hamdy FC, Donovan JL, Lane J, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med. 2016 Oct.;375:1415–1424.
19. Saldanha DF, Khiatani VL, Carrillo TC, et al. Current tumor ablation technologies: basic science and device review. Semin Intervent Radiol. 2010 Sep.;27(3):247-254.
20. van der Poel HG, van den Bergh RC, Briers E, et al. Focal therapy in primary localised prostate cancer: the European Association of Urology position in 2018. Eur Urol. 2018 Jul.;74(1):84–91.
21. Jácome-Pita F, Sánchez-Salas R, Barret E, et al. Focal therapy in prostate cancer: the current situation. Ecancermedicalscience. 2014;8:435.
22. De La Rosette J, Ahmed H, Barentsz J, et al. Focal therapy in prostate cancer—report from a consensus panel. J Endourol. 2010 May;24(5):775–780.
23. Niemz MH. Laser-tissue interactions. Berlin, Heidelberg: Springer; 2007.
24. Huber P, Mann M, Melo L, et al. Focused ultrasound (HIFU) induces localized enhancement of reporter gene expression in rabbit carotid artery. Gene Ther. 2003 Aug.;10(18):1600–1607.
25. van den Bijgaart RJ, Eikelenboom DC, Hoogenboom M, et al. Thermal and mechanical high-intensity focused ultrasound: perspectives on tumor ablation, immune effects and combination strategies. Cancer Immunol Immunother. 2017;66(2):247–258.
26. Khokhlova VA, Fowlkes JB, Roberts WW, et al. Histotripsy methods in mechanical disintegration of tissue: towards clinical applications. Int J Hyperthermia. 2015 Feb.;31(2):145–162.
27. Roberts WW, Hall TL, Cain CA, et al., inventors; The Regents Of The University Of Michigan, assignee. Micromanipulator control arm for therapeutic and imaging ultrasound transducers. W.O. patent 2011028603A2. 2011 March 10.
28. Xu Z, Sukovich J, Pandey AS, et al., inventors; The Regents Of The Universtiy Of Michigan, assignee. Histotripsy therapy systems and methods for the treatment of brain tissue. W.O. patent 2016210133A1. 2016 June 23.
29. Gleiman SS, Mercer NS, O'brien TJ, et al., inventors; Galary, Inc., assignee. Devices, systems and methods for the treatment of abnormal tissue. W.O. patent 2020215007A1. 2020 October 22.
30. Baust J, Gage A, Johansen TB, et al. Mechanisms of cryoablation: clinical consequences on malignant tumors. Cryobiology. 2014 Feb.;68(1):1–11.

31. Roy BN. Fundamentals of classical and statistical thermodynamics. Chichester: John Wiley & Sons; 2002.
32. Surtees B, Mcchesney E, Young S, et al., inventors; The Johns Hopkins University, assignee. Carbon dioxide-based percutaneous cryosurgical system W.O. patent 2019213205A1. 2019 November 17.
•• **Describes clinical aspects and design aspects for a human-centred design.**
33. Zhou L, inventor; Thomas Jefferson University, assignee. Cryoneedle and cryotherapy system. W.O. patent 2008054487A2. 2008 May 8.
34. Korpan N, Zharkov J, inventors; Nikolai Korpan, Jaroslav Zharkov, assignee. Device for carrying out cryosurgical interventions, especially for treating tumors. W.O. patent 2000047121A2. 2000 December 21.
35. Yang C, Xu B, Wu Y, et al., inventors; Accu Target Medipharma (Shanghai) Co., Ltd., assignee. Adjustable cryoablation needle. W. O. patent 2021027397A1. 2021 February 18.
36. Zvuloni R, Amir U, inventors; Galil Medical Ltd., assignee. Apparatus and method for accurately delimited cryoablation W.O. patent 2004086936A2. 2004 October 14.
37. Clarke B, inventor; Nitro Medical Limited, assignee. Cryoablation. W. O. patent WO2018087563A1. 2017 November 10.
38. Davalos RV, Mir L, Rubinsky B. Tissue ablation with irreversible electroporation. Ann Biomed Eng. 2005Feb.;33(2):223.
39. Chu KF, Dupuy DE. Thermal ablation of tumours: biological mechanisms and advances in therapy. Nat Rev Cancer. 2014 Feb.;14(3):199–208.
40. Davalos RV, Arena CB, Caldwell J, inventors; Virginia Tech Intellectual Properties, Inc., assignee. Integration of very short electric pulses for minimally to noninvasive electroporation. W. O. patent 2010118387A1. 2010 October 14.
41. Hobbs EP, Lovewell JG, Pearson RM, inventors; AngioDynamics, Inc., assignee. Irreversible electroporation and tissue regeneration. W.O. patent 2010093692A2. 2010 August 19.
42. Appling WM, William C, Hamilton J, et al., inventors; AngioDynamics, Inc., assignee. Electroporation device and method W.O. patent 2009137800A2. 2009 November 12.
43. Long GL, Ghabrial RM, Plescia DN, et al., inventors; Ethicon Endo-Surgery Inc., assignee. Electrical ablation devices. W.O. patent 2010080974A1. 2010 July 15.
44. Dimitrova T, Weis A. The wave-particle duality of light: a demonstration experiment. Am J Phys. 2008 Jan.;76 (2):137–142.
45. Zamanian A, Hardiman C. Electromagnetic radiation and human health: a review of sources and effects. High Frequency Electronics 2005 Jul.;4(3):16–26.
46. Baskar R, Lee KA, Yeo R, et al. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012Feb.;9(3):193-199.
47. Francescatti D, Lovoi PA, inventors; Xoft, Inc., assignee. Endoscopic/percutaneous electronic radiation applicator and method of use. W.O. patent 2008005435A2 2008.January 10.
48. Fehre J, Granz B, Lanski M, et al., inventors; Siemens Aktiengesellschaft, assignee. Device for x-ray brachytherapy, and method for positioning a probe introduced into a body for x-ray brachytherapy. W.O. patent 2007060049A1. 2007 May 31.
49. Gutman G, Strumban E, inventors; Advanced X-Ray Technology, Inc., assignee. X-ray needle apparatus and method for radiation treatment W.O. patent 2006068671A2. 2005 August 16.
50. Flynn R, Dadkhah H, Patwardhan K, et al., inventors; University Of Iowa Research Foundation, assignee. A rotating shield brachytherapy system W.O. patent 2017184728A1. 2017 October 26.
51. Murray SC, Davenport SA, Coleman T, inventors; Laserscope, assignee. Methods for laser treatment of soft tissue W.O. patent 2002091935A1. 2002 November 21.
52. Ganz RA, inventor; Robert A. Ganz, assignee. Apparatus and method for debilitating or killing microorganisms within the body. W.O. patent 2000078393A1. 2000 December 28.
53. Alvarez A, Lacalle J, Cañavate M, et al. Cell death. A comprehensive approximation. Necrosis. Microsc Science, Technology, Appl Educ. 2010;2:1017–1024.
54. Zhu L, Altman MB, Laszlo A, et al. Ultrasound hyperthermia technology for radiosensitization. Ultrasound Med Biol. 2019;45 (5):1025–1043.
55. Mo S-K, Kim N-T, inventors; Seung-Kee Mo, Nam-Tae Kim, assignee. Device for treating tumor and fat using microwave. W.O. patent 2003103768A1. 2003 December 18.
56. Wang Z, inventor; The University Of Dundee, assignee. Radio frequency surgical probe. W.O. patent 2013076440A1. 2013 May 30.
57. Mulier SMM, Verhaegen G, Mulier MWJ, et al., inventors; Vesalius Medical Technologies Bvba, assignee. Device and method for radio frequency ablation (rfa). W.O. patent 2011113943A1. 2011 September 22.
58. Habib N, inventor; Emcision Limited, assignee. Device and method for the treatment of diseased tissue such as tumours. W.O. patent 2008084244A2. 2008 July 17.
59. Thistle RC, inventor; Boston Scientific Scimed, Inc., assignee. Low-profile, expanding single needle ablation probe. W.O. patent 2007094887A2. 2007 August 23.
60. Mccullagh O, Spiridigliozzi JC, Sauvageau DJ, inventors; Boston Scient Scimed Inc, Spiridigliozzi John C, assignee. Co-access bipolar ablation probe. W.O. patent 2006073879A2. 2006 July 13.
61. Venturelli L, inventor; Fogazzi Di Venturelli, Andrea & C. S.N.C., assignee. Rf hyperthermia with needle electrodes enclosing a volume. W.O. patent 2003090636A1. 2003 November 6.
62. Cockburn JF, Cockburn DJA, Wemyss-Holden S, inventors; The Norfolk And Norwich University Hospital Nhs Trust, assignee. Electro-surgical needle apparatus. W.O. patent 2006082413A1. 2006 August 10.
63. Faure A, inventor; Université de Franche-Comté, assignee. Medical device using a coiled electrode. W.O. patent 2004100812A1. 2004 November 25.
64. Mori K, inventor; Kenji Mori, assignee. Cautery needle device, high frequency cautery therapy system, and chemical cautery therapy system. W.O. patent 2017126265A1. 2017 July 27.
65. O'dea J, Mchugh A, Griffin P, inventors; Flip Technologies Limited, assignee. An ablation system and a device and a method for ablating matter in a lumen or a cavity. W.O. patent 2009001326A1. 2008 December 31.
66. Panescu D, Gelfand M, Leung M, inventors; Zidan Medical, Inc., assignee. Devices for treating lung tumors W.O. patent 2019051274A2. 2019 March 14.
67. Utley DS, Gerberding BC, Taimisto MH, et al., inventors; Barrx Medical, Inc., assignee. System and method for ablational treatment of uterine cervical neoplasia. W.O. patent 2009154654A1. 2009 December 23.
68. Pacey A, Habib N, inventors; Emcision Limited, assignee. Apparatus and method for treating tissue such as tumours W.O. patent 2007135437A1. 2007 November 29.
69. Behl RS, Grosser M, Huang AL, inventors; Radiotherapeutics Corporation, assignee. Methods and systems for focused bipolar tissue ablation W.O. patent 2002022032A1. 2002 March 21.
70. Young K, Zerfas JW, inventors; Boston Scientific Scimed, Inc., assignee. Ablation probe with flared electrodes. W.O. patent 2006049810A1. 2006 May 11.
71. Young K, Bukowski SP, inventors; Boston Scientific Scimed, Inc., assignee. Electrosurgical probe having current enhancing protrusions W.O. patent 2009086409A1. 2009 July 9.
72. Miller BJ, Sherar M, Mccann C, et al., inventors; University Health Network, assignee. Coil electrode for thermal therapy W.O. patent 2012100355A1. 2012 January 30.
73. Xiao B, Qin J, Tang W. inventors; Medsphere International, assignee. Radio-frequency ablation electrode device with double-layer umbrella-shaped probes. W.O. patent 2015051594A1. 2015 April 16.
74. Morris D, Altoukhi K, Valle S, et al. inventors; Ablation Gen 2 Pty Ltd, assignee. Devices and methods for ablating tissue. W.O. patent 2020150782A1. 2020 July 20.

75. Clerck LD, inventor; Medical Development Technologies S.A., assignee. Heatable implant device for tumor treatment. W. O. patent 2019120489A1. 2019 June 27.
76. Hancock CP, Chaudry MS, Goodman AM, inventors; Christopher Paul Hancock, Mohammed Sabih Chaudry, Andrew Marc Goodman, assignee. Tissue ablation apparatus and method of ablating tissue W.O. patent 2004047659A2. 2004 June 10.
77. Hancock CP, White M, Burn P, et al., inventors; Creo Medical Limited, assignee. Electrosurgical probe for delivering microwave energy. W.O. patent 2017103209A1. 2017 June 22.
78. Chornenky V, Swanson V, Hodge RG, et al., inventors; Medtronic Ave Inc, assignee. Hyperthermia radiation apparatus and method for treatment of malignant tumors. W.O. patent 2002045790A2. 2002 June 13.
79. Hancock CP, White M, Burn P, inventors; Creo Medical Limited, assignee. Electrosurgical instrument with impedance transformer for delivering microwave energy. W.O. patent 2016203257A1. 2016 December 22.
80. Tosoratti N, inventor; H.S. - Hospital Service - S.P.A., assignee. Microwave device for the ablation of tissues W.O. patent 2006084676A1. 2006 August 17.
81. Buttar NS, Song L-MWK, Asirvatham SJ, inventors; Mayo Foundation For Medical Education And Research, assignee. Thermal therapy systems and methods. W.O. patent 2016126461A1. 2016 August 11.
82. Hancock P, inventor; Creo Medical, assignee. Electrosurgical apparatus for treating biological tissue with microwave energy. W. O. patent 2021052913A1. 2021 March 25.
83. Pfannenstiel A, Fallahi H, Prakash P, inventors; Kansas State University Research Foundation, Precision Microwave Inc., assignee. Minimally invasive microwave ablation device. W.O. patent 2020242973A1. 2020 December 3.
84. Hancock CP, Taplin W, Ullrich G, et al., inventors; Creo Medical Limited, assignee. Electrosurgical instrument. W.O. patent 2020114878A1. 2020 June 11.
85. Masotti L, inventor; El.En. S.P.A., Esaote S.P.A., assignee. Device for treating tumors by laser thermotherapy. W.O. patent 2005055848A2. 2005 June 23.
86. Dzerins O, Pfafrods D, inventors; Sia Light Guide Optics International, assignee. Device for treatment of body tissue. W. O. patent 2020058447A1. 2020 March 26.
87. Shafirstein G, Ferguson SL, Waner M, inventors; Board Of Trustees Of The University Of Arkansas, assignee. Conductive interstitial thermal therapy device W.O. patent 2004019809A2. 2004 March 11.
88. Huang S-C, Wen H-S, Yang T-F, et al., inventors; Taiwan Earning Co. Ltd., assignee. Tumor ablation system. W.O. patent 2017193938A1. 2017 November 16.
89. Wago T, Shuto B, Iwabuchi A, inventors; Incorporated National University Iwate University, assignee. A drug delivery system using an acupuncture needle. W.O. patent 2013183791A1. 2013 December 12.
90. Fallik J, inventor; Joel Fallik, assignee. 3d microwave system and methods. W.O. patent 2010019840A1. 2010 February 18.
91. Virta TJV, inventor; Koninklijke Philips Electronics N.V., assignee. Ultrasonic treatment apparatus with a protective cover. W. O. patent 2010032186A1. 2010 March 25.
92. Jiang J, Dong J, Ma H, et al. inventors; Shanghai A & S Science Technology Development Co., Ltd., assignee. Hifu tumor ablating system. W.O. patent 2007056905A1. 2007 May 24.
93. Chauhan S, Ng WS, inventors; Nanyang Technological University, assignee. Ultrasonic treatment of breast cancer. W.O. patent 2003059434A2. 2003 July 24.
94. Lacoste F, inventor; Theraclion, assignee. Head for imaging and treating organs of living beings and method for making same. W. O. patent 2006129045A2. 2006 December 7.
95. Quigley DP, Gal A, Phillips MH, inventors; Sono Esthetx, Inc., assignee. Method, system, and apparatus for line-focused ultrasound therapy W.O. patent 2008144274A2. 2008 November 27.
96. Bruggers JW, inventor; Koninklijke Philips Electronics N.V., assignee. Apparatus for thermal treatment of tissue. W.O. patent 2008026134A1. 2008 March 6.
97. Carpentier A, Itzcovitz J, inventors; Alexandre Carpentier, Julian Itzcovitz, assignee. A medical system comprising a percutaneous probe. W.O. patent 2009125002A1. 2009 October 15.
98. Nguyen-Dinh A, Dufait R, Notard C, et al., inventors; Vermon S.A., Carthera S.A.S., Institut National De La Sante Et De La Recherche Medicale (Inserm), Universite Pierre Et Marie Curie (Paris 6), assignee. Interstitial ultrasonic disposable applicator for tissue thermal conformal volume ablation and monitoring the same. W. O. patent 2014141052A1. 2014 September 18.
99. Rem-Bronneberg D, inventor; Koninklijke Philips N.V., assignee. Ultrasound ablation device. W.O. patent 2017144288A1. 2011
100. Lau MPH, Teng N, Vaezy S, et al., inventors; Mirabilis Medica Inc., assignee. Methods and apparatus for the treatment of menometrorrhagia, endometrial pathology, and cervical neoplasia using high intensity focused ultrasound energy. W.O. patent 2007143281A2. 2007 December 13.
101. Bronskill MJ, Chopra R, inventors; Sunnybrook Health Sciences Centre and Women's College Health Sciences Centre, assignee. Technique and apparatus for ultrasound therapy W.O. patent 2002032506A1. 2002 April 25.
102. Carpentier A, Lafon C, Chapelon J-Y, et al., inventors; Universite Pierre Et Marie Curie (Paris 6), Assistance Publique - Hopitaux De Paris, Carthera, assignee. Apparatus for the treatment of brain affections and method implementing thereof. W.O. patent 2011101492A2. 2011
103. Ahmed M, Brace CL, Lee JFT, et al. Principles of and advances in percutaneous ablation. Radiology. 2011 Feb.;258(2):351–369. .
104. Toth L, Schwartz R, inventors; Landy Toth, Robert Schwartz, assignee. Precision chemical ablation and treatment of tissues. W. O. patent 2016014750A1. 2016 January 28.
105. Fischell DR, Fischell TA, Ragland RR, et al., inventors; Ablative Solutions, Inc., assignee. Peri-vascular tissue ablation catheter with support structures W.O. patent 2014070558A1. 2014 May 8.
106. Barnett BP, Gailloud P, Yung RC, inventors; The Johns Hopkins University, assignee. Drug eluting hydrogels for catheter delivery. W.O. patent 2012012772A2. 2012 January 26.
107. Neisz JJ, Escandon MAS, inventors; Ams Research Corporation, assignee. Surgical kit for treating prostate tissue. W.O. patent 2003005889A2. 2003 January 23.
108. Volotskova O, Hawley TS, Stepp MA, et al. Targeting the cancer cell cycle by cold atmospheric plasma. Sci Rep. 2012 Sep.;2:636.
109. Graves DB. Reactive species from cold atmospheric plasma: implications for cancer therapy. Plasma Process Polym. 2014 Aug.;11 (12):1120–1127.
110. Keidar M, Walk R, Shashurin A, et al. Cold plasma selectivity and the possibility of a paradigm shift in cancer therapy. Br J Cancer. 2011 Oct.;105(9):1295–1301.
111. Bartsch H, Nair J. Chronic inflammation and oxidative stress in the genesis and perpetuation of cancer: role of lipid peroxidation, DNA damage, and repair. Langenbecks Arch Surg. 2006 Aug.;391 (5):499–510.
112. Barthel JS, inventor; H. Lee Moffitt Cancer Center & Research Institute, assignee. Endoscopic caps for ionized plasma confinement, shaping and control for therapeutic purposes. W.O. patent 2011022069A2. 2011 February 24.
113. Krasik Y, Felsteiner J, Slutsker Y, et al., inventors; Technion Research & Development Foundation Limited, Rambam Med Tech Ltd., assignee. Cold plasma generating system W.O. patent 2016079742A1. 2016 May 26.
114. Ahdoot M, Lebastchi AH, Turkbey B, et al. Contemporary treatments in prostate cancer focal therapy. Curr Opin Oncol. 2019 May;31(3):200-206.
115. Agostinis P, Berg K, Cengel KA, et al. Photodynamic therapy of cancer: an update. CA Cancer J Clin. 2011 May;61(4):250–281.
116. Dolmans DE, Fukumura D, Jain RK. Photodynamic therapy for cancer. Nat Rev Cancer. 2003 May;3(5):380–387.
117. Dougherty TJ, Gomer CJ, Henderson BW, et al. Photodynamic therapy. JNCI. 1998 Jun.;90(12):889–905.
118. Chen JC, Keltner L, Naimushin AN, inventors; James C. Chen, Llew Keltner, Alexei N. Naimushin, assignee. Systems, devices, and

methods for tissue therapy. W.O. patent 2016040383A1. 2016 March 17.
- **Provides a mechanical solution to destroy the cell structure using combined energy and matter.**

119. Rylander CG, Kosoglu MA, Hood RL, et al., inventors; Virginia Tech Intellectual Properties, Inc., assignee. Fiber array for optical imaging and therapeutics W.O. patent 2012154284A2. 2012 November 15.
120. Patrice T, Neuberger W, Bode H-P, et al., inventors; Ceramoptec Industries, Inc., assignee. Treatment for epithelial diseases W. O. patent 2002007630A1. 2002 January 31.
121. Shang H, inventor; Beijing Yestarpatent Agency co., Ltd, assignee. Photodynamic therapy and diagnosis device capable of optical fiber puncturing. W.O. patent 2020019305A1. 2020 January 30.
122. Schultheis B, Keiper O, Meinl J, et al., inventors; Ag, Schott;, assignee. Illumination system having an optical waveguide with substantially radially emitting diffuser element, and method for production thereof. W.O. patent 2020127762A2. 2020 June 25.
123. Maeda H, inventor; Hiroshi Maeda, assignee. Light radiating probe for photodynamic therapy employing endoscope. W.O. patent 2018092814A1. 2018 May 24.
124. Chen JC, Barnard WL, Shine DB, et al., inventors; Light Sciences Oncology, Inc., assignee. Low-profile intraluminal light delivery system and methods of using the same. W.O. patent 2011020064A2. 2011 February 17.
125. Chen J, Christophersen J, Yeo N, et al., inventors; Light Sciences Corporation, assignee. Systems and methods for photodynamic therapy. W.O. patent 2003061696A2. 2003 July 31.
126. Rogers GS, inventor; Gary S. Rogers, assignee. Continuous low irradiance photodynamic therapy system and method. W. O. patent 2007146101A2. 2007 December 21.
127. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens —part D: radiation. Lancet Oncol. 2009 Aug.;10(8):751–752.
128. Kelson I, Keisari Y, Schmidt M, et al., inventors; Alpha Tau Medical Ltd., assignee. Controlled release of radionuclides. W.O. patent 2019193464A1. 2019 October 10.
129. Kelson I, Keisari Y, Schmidt M, et al., inventors; Alpha Tau Medical Ltd., assignee. Radiotherapy seeds and applicators. W.O. patent 2019171308A1. 2019 September 12.
130. Kelson I, Arazi L, inventors; Ramot At Tel Aviv University Ltd., assignee. Method and device for radiotherapy. W.O. patent 2004096293A2. 2004 November 11.
131. Nakaji P, Brachman D, Mcbride H, et al., inventors; Theresa, Thomas, assignee. Dosimetrically customizable brachytherapy carriers and methods thereof in the treatment of tumors W.O. patent 2012149580A1. 2012 November 1.
132. Desantis M, Cipriani C, inventors; Maria Desantis, Cesidio Cipriani, assignee. Composition, device and method for conformational intra-tissue beta branchytherapy. W.O. patent 2018138744A1. 2018 August 2.
133. Halpern DS, inventor; Isotron, Inc., assignee. Neutron brachytherapy device and method. W.O. patent 2001019450A2. 2001 March 22.
134. Chen S-W, inventor; Empire Technology Development Llc, assignee. Method and system for radioisotope ion beam gamma therapy. W. O. patent 2012030297A1. 2012 March 8.
135. Tanrisever NE, inventor; Naim Erturk Tanrisever, assignee. Plasma arc sur surgical device and method. W.O. patent 2002030308A1. 2002 April 18.
136. Sersa G, Miklavcic D, Cemazar M, et al. Electrochemotherapy in treatment of tumours. Eur J Surg Oncol. 2008 Feb.;34(2):232–240.
137. Rodriguez JF, Phung BD, Twitty CG, et al., inventors; Oncosec Medical Incorporated, assignee. Electroporation systems, methods, and apparatus W.O. patent 2019213421A1. 2019 November 7.
138. Chen Y, inventor; Hangzhouready Biological Technology Co., Ltd, assignee. Electric pulse ablation device capable of synergistic administration W.O. patent 2020232849A1. 2020 November 26.
139. Schroeppel EA, Kroll MW, Kroll K, inventors; Edward A. Schroeppel, Mark W. Kroll, Kai Kroll, assignee. Method and device for treating concer with electrical therapy in conjunction with chemotherapeutic agents and radiation therapy. W.O. patent 2004037341A2. 2004 May 6.
140. Davalos RV, Rylander MN, Arena CB, inventors; Virginia Tech Intellectual Properties, Inc., assignee. Irreversible electroporation using nanoparticles. W.O. patent 2010151277A1. 2010 December 29.
141. Soikum S, Thomsen L, Dodgson JR, inventors; Giantcode Corporation Pte Ltd, assignee. Method, device and system for targetted cell lysis. W.O. patent 2011135294A1. 2011 April 26.
142. Liang P, inventor; Ping Liang, assignee. Methods for killing cancer cells and cellular imaging using magneto-electric nano-particles and external magnetic field. W.O. patent 2016025768A1. 2016 February 18.
143. Eggers PE, Thapliyal HV, inventors; Arthrocare Corporation, assignee. Systems and methods for electrosurgical treatment of tissue in the brain and spinal cord W.O. patent 2000007507A1. 2000 February 17.
144. Long GL, Plecia DN, Shires PK, inventors; Ethicon Endo-Surgery, Inc., assignee. Electrical ablation devices. W.O. patent 2011081996A2. 2011 July 7.
145. Schumann C, Hetzel M, Babiak AJ, et al. Endobronchial tumor debulking with a flexible cryoprobe for immediate treatment of malignant stenosis. J Thorac Cardiovasc Surg. 2010 Apr.;139 (4):997–1000.
146. Au JT, Carson J, Monette S, et al. Spray cryotherapy is effective for bronchoscopic, endoscopic and open ablation of thoracic tissues. Interact Cardiovasc Thorac Surg. 2012 Oct.;15(4):580–584.
147. Krimsky WS, inventor; Reset Medical, Inc., assignee. Method for cryospray ablation in reproductive tissues. W.O. patent 2010118325A2. 2010 October 14.
148. Johnston MH, inventor; Mark H. Johnston, assignee. Tracheobronchial pulmonary cryogenic therapeutic method and apparatus. W.O. patent 2010117777A2. 2010 October 14.
149. Field LA, Gerlach D, inventors; Empire Technology Development Llc, assignee. Devices and techniques for ablative treatment W. O. patent 2015099786A1. 2015 July 2.
150. Hoey M, Mauch G, Schrom M, inventors; Nxthera, Inc., assignee. Systems and methods for treating prostate cancer. W.O. patent 2014153082A2. 2014 September 25.
151. Carmel Y, Wyk RV, Shkavarunets A, inventors; Electromedical Associates Llc, assignee. Devices and methods for ablating and removing a tissue mass. W.O. patent 2009131928A1. 2009 October 29.
152. Ruse RB, Bohanan SJ, Crawford ED, et al., inventors; Richard B. Ruse, Scott J. Bohanan, E. David Crawford, William L. Nabors, assignee. Method and apparatus for treating cancer W.O. patent 2013022939A1. 2013 February 14.
153. Kubota S, inventor; Shigehiro Kubota, assignee. Laser therapy method, highly laser beam-absorbing media to be used in the therapy and laser therapy apparatus with the use of the same. W. O. patent 2002036201A1. 2002 May 10.
154. Myhr G, inventor; Cancercure As, assignee. Therapeutic probe, method and system. W.O. patent 2005002671A1. 2005 January 13.
155. Theuer AE, inventor; Gerhard Franz Walter, assignee. Medical device for treating tumor tissue. W.O. patent 2010049176A1. 2010 May 6.
156. Hobbs EHO, Gary M, Miessau JA, et al., inventor; Hobbs, Eamonn; Onik, Gary M; Miessau, James A; Condra, Jon H, assignee. In situ therapeutic cancer vaccine creation system and method. W. O. patent 2020131885A1. 2020 June 25.
157. Fomitchev-Zamilov MI, Hymer W, Kosik A, inventors; Quantum Cure, Inc., Quantum Vortex, Inc., assignee. Method and apparatus for cancer treatment. W.O. patent 2014204978A1. 2014 December 24.
158. Lamb KJ, inventor; Karl J. Lamb, assignee. System and method for hyperthermic tumor treatment. W.O. patent 2012006290A2. 2012 January 12.
159. Handy ES, Ivkov R, Ellis-Busby D, et al., inventors; Triton Biosystems Inc., assignee. Thermotherapy via targeted delivery of nanoscale magnetic particles. W.O. patent 2003022360A2. 2003 March 20.

160. Goodrich GP, Schwartz JA, Murphy AM, inventors; Nanospectra Biosciences, Inc., assignee. Devices and the use thereof in methods for ablation therapy W.O. patent 2018112261A1. 2018 June 21.
161. Kislev H, inventor; Kpe Ltd., assignee. Nanoparticle mediated ultrasound therapy and diagnostic imaging. W.O. patent 2006051542A1. 2006 May 18.
162. Peyman GA, inventor; Gholam A. Peyman, assignee. Cancer treatment methods using thermotherapy and/or enhanced immunotherapy. W.O. patent 2019071261A1. 2019 April 11.
163. Srimathveeravalli G, Reiner T, Solomon S, inventors; Memorial Sloan Kettering Cancer Center, assignee. Systems and methods for enhancing delivery of diagnostic and/or therapeutic compositions in vivo using electric pulses. W.O. patent 2017173089A1. 2017 October 5.
164. Baron E, inventor; I-Check, Inc, assignee. Integrated system for noninvasive focused energy treatment using energy activated drugs. W.O. patent 2006030534A1. 2006 March 23.
165. Copty A, inventor; Synergymed Devices Inc., assignee. Precise ablation treatment of cancer using synergetic effects of electromagnetic radiation with nanoparticles. W.O. patent 2020141527A1. 2020 July 9.
166. Koning GA, Eggermont AM, Lindner LH, et al. Hyperthermia and thermosensitive liposomes for improved delivery of chemotherapeutic drugs to solid tumors. Pharm Res. 2010 Apr.;27 (8):1750–1754.
167. Mon J, inventor; Boston Scientific Corporation, assignee. Method of treating cancer comprising introduction of heat and delivery of liposome containing an active agent or thermo-activated drug, gene or virus to tissue. W.O. patent 2008039188A1. 2008 April 3.
168. Fenn AJ, Mon J, Smith D, inventors; Celsion Corporation, assignee. Monopole phased array thermotherapy applicator for deep tumors W.O. patent 2004022159A1. 2004 March 18.
169. Vishwanath GV, inventor; Sbf Healthcare Private Limited, assignee. Sequentially programmed magnetic field therapeutic system (spmf). W.O. patent 2010095147A2. 2010 August 26.
• **Describes the biological effects inside the body as result of the therapy provided by the design.**
170. Blackiston DJ, McLaughlin KA, Levin M. Bioelectric controls of cell proliferation: ion channels, membrane voltage and the cell cycle. Cell Cycle. 2009 Nov.;8(21):3527–3536.
171. Sano MB, Arena CBA, Verbridge SS, et al., inventors; Virginia Tech Intellectual Properties, Inc., assignee. Selective modulation of intracellular effects of cells using pulsed electric fields. W.O. patent 2015175570A1. 2015 November 19.
172. Fajardo LF, Egbert B, Marmor J, et al. Effects of hyperthermia in a malignant tumor. Cancer. 1980 Feb.;45(3):613–623.
173. Willis W, Jackman M, Bizeau M, et al. Hyperthermia impairs liver mitochondrial function in vitro. Am J Physiol Regul Integr Comp Physiol. 2000 May;278(5):R1240–R1246.
174. Kolvenbag GJ, Blackledge GR, Smith K. Bicalutamide (Casodex®) in the treatment of prostate cancer: history of clinical development. Prostate. 1998 Dec.;34(1):61–72.
175. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. Jama. 2005 Jul.;294(2):238–244.
176. Osborne CK. Tamoxifen in the treatment of breast cancer. N Engl J Med. 1998 Nov.;339(22):1609–1618.
177. Denekamp J. Vascular attack as a therapeutic strategy for cancer. Cancer Metast Rev. 1990 Nov.;9(3):267–282.
178. Habib N, inventor; Emcision Ltd, Nagy Habib, assignee. Vessel sealing device and methods. W.O. patent 2007135431A2. 2007 November 29.
179. Gat Y, Goren M, inventors; Yigal Gat, Menachem Goren, assignee. Methods and apparatus for treating the prostate. W.O. patent 2009010964A2. 2009 January 22.
• **Presents a design to treat prostate cancer by occluding an internal spermatic vein.**
180. Barry RLB, Henne EM, inventors; Intuitive Surgical Operations, Inc., assignee. Systems and methods for localized endoluminal thermal liquid treatment. W.O. patent 2021007255A1. 2021 January 14.
181. Gray J, Zamarripa N, inventors; Boston Scientific Scimed, Inc., assignee. Occlusion device detachable by inflation of a balloon. W.O. patent 2015120155A1. 2015 August 13.
182. Parsons JE, Connolly MJ, Darlington GP, et al., inventors; Mirabilis Medica, Inc., assignee. Method and apparatus for treating tissues with hifu. W.O. patent 2010040140A2. 2010 April 8.
183. Connors KG, Schutt EG, Gillespie J, et al., inventors; Attenuex Technologies, Inc., assignee. Implant with high vapor pressure medium W.O. patent 2010068467A1. 2010 June 17.
184. Ken CGM, Patel TJ, inventors; Concentric Medical, assignee. Device for vaso-occlusion. W.O. patent 2003037191A1. 2003 May 8.
185. BostonScientific.com. VISUAL ICE™ Cryoablation Needles [cited 2020 Apr 8]. Available from: https://www.bostonscientific.com/en-US/products/cryoablation/visual-ice/visual-ice-cryoablation-needles.html.
186. BostonScientific.com. VISUAL ICE™ Cryoablation System [cited 2020 Apr 8]. Available from: https://www.bostonscientific.com/en-US/products/cryoablation/visual-ice.html
187. HealthTronics.com. Endocare™ precision cryoprobes [cited 2020 Apr 8]. Available from: https://www.healthtronics.com/wp-content/uploads/2017/02/Cryoprobe-Brochure-Rev-E_opt.pdf
188. Lau B, Shah TT, Valerio M, et al. Technological aspects of delivering cryotherapy for prostate cancer. Expert Rev Med Devices. 2015 Jan.;12(2):183–190.
189. Wendler JJ, Porsch M, Fischbach F, et al. Letter to the Editor Concerning" Irreversible Electroporation (IRE) Fails to Demonstrate Efficacy in a Prospective Multicenter Phase II Trial on Lung Malignancies: the ALICE Trial" by Ricke et al. Cardiovasc Intervent Radiol. 2015;38(4):1064-1065.
190. AngioDynamics.com. NanoKnife 3.0 System [cited 2020 Apr 8]. Available from: https://www.angiodynamics.com/products/2/The-NanoKnife-System/
191. AngioDynamics.com. NanoKnife 3.0 Irreversible Electroporation (IRE) [cited 2020 Apr 8]. Available from: https://www.angiodynamics.com/img/resources/ANGB_1070_US_REV_01_NanoKnife_3.0-Web-586599.pdf
192. Silk M, Tahour D, Srimathveeravalli G, et al., The state of irreversible electroporation in interventional oncology. Semin Intervent Radiol.; 2014 Jun.;31(2):111–117.
193. Jourabchi N, Beroukhim K, Tafti BA, et al. Irreversible electroporation (NanoKnife) in cancer treatment. Gastrointestinal Intervention. 2014 Jun.;3(1):8–18.
194. BostonScientific.com. LEVEEN™ Needle Electrodes [cited 2020 Apr 8]. Available from: https://www.bostonscientific.com/content/dam/bostonscientific/pi/portfolio-group/rfa/RF_3000_LeVeen%20Needle%20Sell%20Sheet%20(PI-323104-AA).pdf
195. Medtronic.com. Cool-tip™ RF Ablation System E Series [cited 2020 Apr 8]. Available from: https://www.medtronic.com/covidien/en-us/products/ablation-systems/cool-tip-rf-ablation-system-e-series.html
196. AngioDynamics.com. StarBurst® XL & Semi-Flex RFA Devices [cited 2020 Apr 8]. Available from: https://www.angiodynamics.com/products/6/StarBurst-XL-Semi-Flex-RFA-Devices/
197. AngioDynamics.com. Solero microwave tissue ablation system [cited 2020 Apr 8]. Available from: https://www.angiodynamics.com/img/resources/Solero_Product_Brochure-092167.pdf
198. ProfoundMedical.com. TULSA-PRO [cited 2020 Apr 8]. Available from: https://profoundmedical.com/new-tulsa/
199. ProfoundMedical.com. The Sonalleve system [cited 2020 Apr 8]. Available from: https://profoundmedical.com/sonalleve/
200. Philips.nl. Sonalleve MR-HIFU Therapy platform [cited 2020 Apr 8]. Available from: https://www.philips.nl/healthcare/product/HC781360/sonalleve-mr-hifu
201. edap-tms.com. Focal One Focal HIFU for Prostate Cancer [cited 2020 Apr 8]. Available from: https://www.edap-tms.com/en/products-services/prostate-cancer/focal-one
202. edap-tms.com. Ablatherm HIFU Non-invasive treatment for prostate cancer [cited 2020 Apr 8]. Available from: https://www.edap-tms.com/en/products-services/prostate-cancer/ablatherm-hifu

203. Sonacaremedical.com. Sonablate HIFU targeted prostate ablation [cited 2020 Jun 22]. Available from: https://sonacaremedical.com/surgeons/our-products/sonablate
204. Cramers P, Ruevekamp M, Oppelaar H, et al. Foscan® uptake and tissue distribution in relation to photodynamic efficacy. Br J Cancer. 2003 Jan.;88(2):283–290.
205. Azzouzi A-R, Vincendeau S, Barret E, et al. Padeliporfin vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer (CLIN1001 PCM301): an open-label, phase 3, randomised controlled trial. Lancet Oncol. 2017 Apr.;18(2):181–191.
206. Applied-Optronics.com. High power laser diodes fiber coupled package [cited 2020 Apr 8]. Available from: http://www.applied-optronics.com/pdf/4.pdf
207. IGEA.it. Cliniporator [cited 2020 Apr 8]. Available from: https://www.igea.it/sites/default/files/CLINIPORATOR/CLINIPORATOR_SIMPLE%20SOLUTION_ENG_IGEAE0130418.pdf
208. Rebersek M, Miklavcic D, Bertacchini C, et al. Cell membrane electroporation-Part 3: the equipment. IEEE Electrical Insulation Magazine. 2014;30(3):8–18.
209. Mulier S, Miao Y, Mulier P, et al. Electrodes and multiple electrode systems for radiofrequency ablation: a proposal for updated terminology. Eur Radiol. 2005 Feb.;15(4):798–808.
210. Chauhan VP, Stylianopoulos T, Martin JD, et al. Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner. Nat Nanotechnol. 2012;Apr.;7(6):383-388.
211. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971 Nov.;285(21):1182–1186.
212. Folkman J. Fighting cancer by attacking its blood supply. Sci Am. 1996 Sep.;275(3):150–154.
213. Witte MH, Jones K, Wilting J, et al. Structure function relationships in the lymphatic system and implications for cancer biology. Cancer Metast Rev. 2006 Jun.;25(2):159–184.
214. Westwood J. Anatomical and physiological models for surgical simulation. Medicine Meets Virtual Reality. 1999;62(999):23.
215. Cha S. Update on brain tumor imaging: from anatomy to physiology. Am J Neuroradiol. 2006 Mar.;27(3):475–487.
216. Giedd JN. The teen brain: insights from neuroimaging. J Adolesc Health. 2008 Apr.;42(4):335–343.
217. Sankineni S, Osman M, Choyke PL. Functional MRI in prostate cancer detection. Biomed Res Int. 2014. DOI:10.1155/2014/590638
218. Nie S. Understanding and overcoming major barriers in cancer nanomedicine. Nanomedicine. 2010 Jun.;5(4):523–528.
219. Stern ST, McNeil SE. Nanotechnology safety concerns revisited. Toxicol Sci. 2008 Jun.;101(1):4–21.
220. Barry SE. Challenges in the development of magnetic particles for therapeutic applications. Int J Hyperthermia. 2008 Mar.;24(6):451–466.
221. Chiang HA, Haleblian GE. Prostate Cancer Imaging: An Engineering and Clinical Perspective. Boca Raton, London, New York: CRC Press; 2018. Chapter 6, Current Role of Focal Therapy for Prostate Cancer; p.53-62.
222. DeSantis CE, Ma J, Jemal A. Trends in stage at diagnosis for young breast cancer patients in the United States. Breast Cancer Res Treat. 2019;173(3):743–747.
223. Van Den Bos W, Muller BG, Ahmed H, et al. Focal therapy in prostate cancer: international multidisciplinary consensus on trial design. Eur Urol. 2014 Jun.;65(6):1078–1083.
224. Carmeliet P, Jain RK. Angiogenesis in cancer and other diseases. nature. 2000 Sep.;407(6801):249–257.
225. Wehbi E, Musquera M, Alcaraz A, et al. Focal Therapy Will Be the Future Treatment Modality: the Motion "Con." Eur Urol Suppl. 2009 Apr.;8(5):433–438.
226. Cserni G, Bori R, Sejben I, et al. Unifocal, multifocal and diffuse carcinomas: a reproducibility study of breast cancer distribution. Breast. 2013 Feb.;22(1):34–38.
227. Coombs NJ, Boyages J. Multifocal and multicentric breast cancer: does each focus matter? J clin oncol. 2005 Oct.;23(30):7497–7502.
228. Karavitakis M, Ahmed HU, Abel PD, et al. Tumor focality in prostate cancer: implications for focal therapy. Nat Rev Clin Oncol. 2011;8(1):48-55.
229. Meiers I, Waters DJ, Bostwick DG. Preoperative prediction of multifocal prostate cancer and application of focal therapy: review 2007. Urology. 2007 Dec.;70(6):S3–S8.
230. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science. 2005 Jan.;307(5706):58–62.
231. Bergers G, Hanahan D. Modes of resistance to anti-angiogenic therapy. Nat Rev Cancer. 2008 Aug.;8(8):592–603.
232. Turkbey B, Pinto PA, Choyke PL. Imaging techniques for prostate cancer: implications for focal therapy. Nat Rev Urol. 2009;Apr.;6(4):191-203.
233. ASTM F2503-13. Standard practice for marking medical devices and other items for safety in the magnetic resonance environment. West Conshohocken, PA: ASTM International; 2013.
234. Kanal E, Barkovich AJ, Bell C, et al. ACR guidance document on MR safe practices: 2013. J Magn Reson Imaging. 2013 Jan.;37(3):501–530.
235. McCulloch P, Cook JA, Altman DG, et al. IDEAL framework for surgical innovation 1: the idea and development stages. Bmj. 2013;346:f3012.