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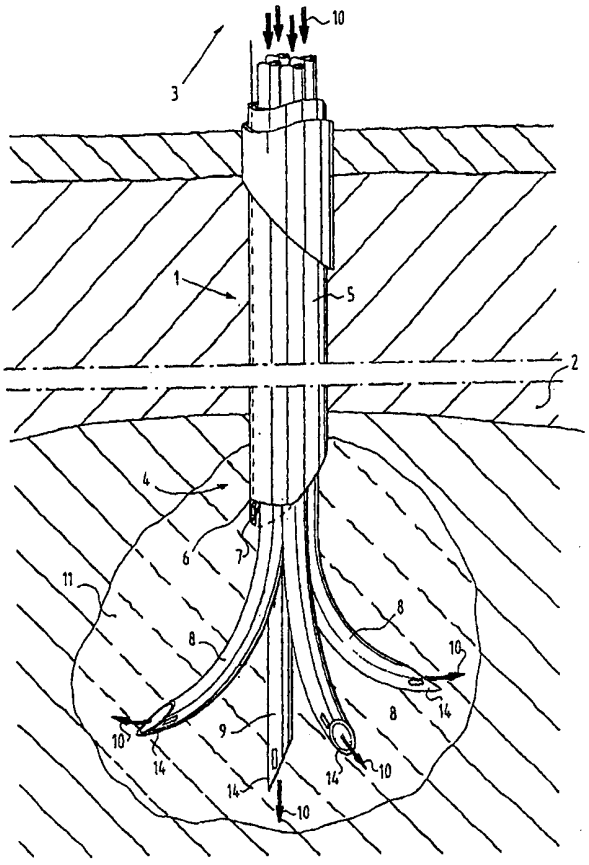
(54) Title: EXPANDABLE WET ELECTRODE

(57) Abstract

The invention relates to a device for delivering radio–frequence (RF) energy (1), for example during tissue ablation procedures, comprising a delivery catheter (5) with a distal end (4) and a proximal end (3) and an electrode deployment device positioned at least partially in the delivery catheter (5) including a plurality of retractable electrodes (8, 9), each electrode having a non–deployed state when positioned within the delivery catheter and a distented deployed state when advanced from the distal end of the delivery catheter defining an ablation volume between the deployed electrodes, said device further comprises wetting means for wetting the proximity of the distal end of the electrode and adjacent tissue with a non–toxic (RF) conductive solution.



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EXPANDABLE WET ELECTRODE

The invention relates to novel devices for delivering radio frequency energy, for example during tissue ablation procedures.

The invention relates in particular to a novel concept of a electrode for the optimization of radio-frequency ablation. This concept will hereunder be nominated as the expandable wet electrode.

Although surgical resection is still considered as a primary option for the treatment of malignant tumors, minimally invasive alternatives including intraoperative cryosurgery, local injection of ethanol, microwaves, interstitial laser therapy focused ultrasound and radio frequency (RF) tissue ablation have been developed in order to ablate the tumor less invasively for the safety of the patient and reduction of the costs and/or to broaden our capability in treatment of the patient.

Among these approaches, RF ablation has shown the greatest impact on recent experimental and clinical research because of its low invasiveness, simplicity and favorable cost-effectiveness.

In RF ablation the radio-frequency waves are emitted from a generator through an uninsulated part of the electrode which is inserted into a target tissue. The tissue destruction in a form of coagulation necrosis is caused primarily by resistive heating in the surrounding tissue and secondarily by the peripheral passive heat conduction.

Resistive heating is proportional to the square of the distance between the central electrode and adjacent tissue. Therefore, significant resistive heating only occurs within a rim of tissue in direct contact with the electrode. Beyond this rim, the tissue is further heated as a result of passive conduction of increased temperature. However, the RF emission is readily terminated as a result of impedance rise at the electrode-tissue interface, which is secondary to tissue desiccati-

on and carbonization. Due to such non-optimal RF energy delivery and dissipation, the lesion size induced by this prototype electrode was smaller than 2 cm, which is obviously insufficient for tumor ablation. Similar to the principle in surgical resection, the ideal range of RF tissue destruction should involve the entire tumor and a layer of adjacent normal tissue as a safety margin to avoid incomplete ablation.

Many known technical innovations have been made to increase the lesion size in RF ablation. These include the introductions of:

1) bipolar electrodes;

2) a cooled electrode;

3) a "wet" electrode with hypertonic saline infusion; and

4) an expandable electrode.

As shown in table 1, although markedly increased, the lesion sizes induced by these modified devices are still limited, normally less than 4 cm in diameter. If a tumor larger than 2 cm, there is little chance to achieve complete ablation by a single session. Therefore there is still a demand to further optimize these devices and techniques.

Table 1 shows the lesion sizes induced by different known designs of electrode in RF Ablation.

Table 1

Electrode Type	Lesion size (cm)*	No. Reference
Prototype Electrode	0,8 - 1,5	1
Bipolar Electrode	5 (the width between poles)**	2
Cooled Electrode	1,4 - 3,6	3
Wet Electrode	4,5 ±0,75	4
Expandable electrode	4,5	5,6

References cited are:

1. Goldberg, S.N. et al. (Academic Radiology 1995;2:

399-404)

2. Goldberg, S.N. et al. (Acad. Radiol. 3/929, 1996)
3. Lorentzen, T.A. (Acad. Radiol. 3:556, 1996)
4. Miao, Y. et al. (J. Surg. Res. 71:19, 1997)
5. Rossi, S. et al. (AJR. Am. J. Roentgenol., 170: 1015-1022, 1998)
6. Patterson EJ, et al. (Ann Surg, 227:559-565, 1998).

The main object of the invention is to provide a new device and methods yielding good RF ablation results and providing larger lesion size. In particular whereby the lesion size is larger than 5 and preferably more than 6 cm.

According to the invention this is realized by a combination of separately known features, which in combination surprisingly results in an effective RF ablation. This is realized by an increased conductivity of the target tissue at the electrode tissue interface with hypertonic saline infusion in combination with expandable electrodes.

The invention therefore provides a device for delivering radio-frequency energy combining the characteristics of a "wet" electrode and of an expandable electrode.

In achieving the above mentioned objects the invention provides a device according to claim 1. The preferred embodiments are defined in the subclaims 2 to 7.

A main object is a minimal invasiveness of the radio-frequency ablation technique. A minimal invasiveness is obtained by a shaft puncturing towards the tissue to be treated. It is therefore a further object of the invention to improve the efficiency of the introduction of the radio-frequency electrode. The introduction is presently performed by the sharpened distal end of the electrode. As this distal end is often open introduction sometimes causes obstruction once introduced and blocks off these distal openings.

As a solution to this disadvantage the invention provides further a guidance element for the guidance of an instrument, in particular a radio-frequency electrode once introduced and longitudinally displaced in said element. The guidance element according to the invention is substantially formed by a open hollow shaft having a cilindrical bore which is adapted in dimensions for the temporarily housing of an instrument during radio-frequency ablation procedures. Said instrument can be for example a puncturing needle for a smooth introduction towards the tissue to be treated, a radio-frequency electrode for the radio-frequency ablation step and further a biopsy needle or biopsy clamp for providing proof of the efficiency of the radio-frequency ablation procedure.

The invention further relates to the use of a device according to the invention as claimed in claim 8 and to a method as defined in claims 9-10.

The invention shall be elucidated with reference to the drawing wherein:

figure 1 shows a partially broken away perspective schematic view of an embodiment of the expandable wet electrode of the invention;

figure 2 shows a schematic illustration of a radio-frequency ablation method with the expandable wet electrode of the invention;

figure 3 is a schematic view of the distal end of the expandable wet electrode of the embodiment depicted in figure 1 in a retracted status; and

figure 4 shows a partial broken away perspective view of a guidance element (figure a), a puncturing needle (figure b) and a biopsy needle (figure c).

The electrode 1 depicted in Fig. 1 shall hereunder be defined as an expandable wet electrode.

The device 1 for delivering radio-frequency energy to a target tissue 2 comprises a proximal end 3 which is connectable to a radio-frequency energy source and a distal end 4. The device comprises a delivery

catheter 5 which is formed by a hollow shaft and which is preferably associated at its distal part 6 with tissue puncturing means 7. In the delivery catheter 5 multiple, here four electrodes 8, 9 are housed having the form of retractable hollow needle electrodes, of which one is straight (9) and three (8) are radially extending when protuding through the delivery catheter 5. Arrows 10 define a flow part for a radio-frequency conductive solution, such as a 5% saline solution, through the hollow channel of the electrodes 8, 9. The wetting solution 11 is delivered in the proximity of the distal end 14 of each electrode 8, 9.

In order to further enlarge the lesion size a cooling solution could be provided to cool at least the distal end of each electrode 8.

In order to create a smoother puncturing, puncturing means 7 are further provided at the distal end of the delivery catheter 5 and/or each distal end of the electrode is also sharpened. A precise temperature control is achieved by providing temperature sensors 20 at the end of each tip of each electrode 8, 9.

The advantages and the specific characteristics of the expandable wet electrode are founded on the following experiments.

Figure 2 shows a schematic illustation of the radio-frequency ablation method using the expandable wet electrode 1 which is at its proximal end 3 connected to a radio-frequency source 17 and wetting means comprising a circulation pump 15 providing circulation from the wetting solution container 13 via the proximal end 3 of the electrode 1 towards the to be treated tumor 19 in the target tissue 2. A ground path 18 closes the radio-frequency electric circuit.

Figure 3 is an enlarged view of the distal end 6 of the electrode 1 showing the four electrodes 8, 9 in a retracted position.

Guidance element 100 is substantially formed by an open elongated shaft 101 provided with a central

cilindrical bore 102 and a open blunt distal end 103. The diametre of the cilindrical bore 102 is thus adjusted that instruments to be guided by the guidance element 100 can be introduced and be displace in the longitudinal direction of the bore for the minimum of radial tolerance but still providing smooth longitudinal guidance. The introduction can preferably be performed by a puncturing needle 104 which is introduced in the guidance element 100 and provided with a sharpened distal end 106 being used as a puncturing mean for introducing the combination guidance element 100 and needle 104 towards to the tissue to be treated. A smooth introduction can be obtained due to the sharpness and to the form and dimensions of the needle 104. Once introduced the needle 104 is retracted out of the cilindrical bore 102 of the guidance element 100 while maintaining the introduced position of the guidance element 100. A radio-frequency electrode can then be introduced through the cilindrical bore 102 of the guidance element 100 and when the radio-frequency ablation procedure is terminated, being retracted out of the guidance element 100, while still maintaining the previous obtained position.

For providing proof of the efficiency of the radio-frequency ablation a biopsy needle 109 can be introduced through the same cilindrical bore towards the treated tissue and the electrode is retracted out of the guidance element 100. The distal end of the biopsy needle 109 is provided with a clamp 108 for collecting treated tissue samples for further investigation. These devices provide further advantages for use of radio-frequency ablation techniques.

A preferred expandable wet electrode should preferably be composed of a stainless steel needle shaft of appropriate length (e.g. 10 to 25 cm) and certain external diameter (e.g. 1,5 to 2.5 mm) insulated by surface material, except distal needle tip of less than 10 mm, three or more hook-shaped retractable fine hollow needles, made of certain alloy (e.g. nickel-titanium) at

a certain angle to each other when they are in expanded status; with or without one straight retractable fine hollow needle. The above hook-shaped and straight needles are bonded together and can be deployed and retracted through the shaft manually or automatically by moving a graduated control mechanism on the handle of the needles. In order to monitor the temperature change of the RFA lesion and to facilitate temperature control mode, a thermocouple can be fixed onto the distal part of the needle shaft.

The materials and methods of the RF experiments comprises beef livers about 10 kilograms each purchased from a local butcher. The temperature of the liver was warmed up from 4°C to room temperature before RF ablation.

The used equipment comprised a demo RF generator (RFG-3E, Radionics, USA), Saline infusion pump (Ismatic, Switzerland).

The experimental groups were:

1. Group A: RFA with expandable "dry" electrodes (without hypertonic saline infusion), 20 sites of ablation (RFA at 50 W for 1-3 min).

2. Group B: RFA with expandable "wet" according to the invention (hypertonic saline infused) electrodes, 20 sites of ablation (RFA at 50 W for 10 min).

3. Group C: RFA with expandable "wet" according to the invention (hypertonic saline infused) electrodes, 10 sites of ablation (RFA at 70-90W for 30 min).

The RFA results with beef livers are summarized in table 2. RFA with expandable "dry" electrode (Group 1) at 50W created averaged lesion size of 3,5 cm. The lesion could not be further enlarged as a result of sudden increase of impedance and decrease of power output within 3 minutes. On the contrary, RFA at 50 W in Group B with expandable "wet" (hypertonic saline infused) electrodes could be easily conducted for longer than 10 minutes. The lesion size is above 6 cm in average. When RFA duration

was prolonged to 30 min and the power was set to 70-90 W, the lesion size was reached as large as above 10 cm.

Table 2

RFA Lesion Sizes between Group A, B and C

Group	No. Sites	Saline Infusion (ml/min)	Lesion Size (cm)
A	20	0	3,5 ±0.4
B	20	1.5	6.3 ±0.6
C	10	1.5	8:9 ±1.2

Based on the previous experiences of using different types of existing electrodes, the present expandable-hollow electrodes have been developed for RFA. In RFA with expandable-dry electrodes, the RF energy is delivered via 3-4 hook-shaped retractable electrodes into a comparable large volume of tissue, leading to a increased lesion size. However, the lesion size can no longer be further increased, because steaming and tissue desiccation occur next to the electrode-tissue interface of each electrode which causes a rise of impedance and a cease of RF current delivery. Besides, the shape of the lesion of this mode is not spherical but irregular, i.e. 3- or 4-petalled shape.

In RFA with expandable wet electrodes, hyperconductive saline is prior and continuously infused via each hollow electrode into the target tissue while RF energy is delivered. The conductivity of 0.9 % normal saline is 3-5 times higher than that of the blood and 12-15 times higher than that of tissues. With more than 5 times of increased concentration, further improvement of conductivity can be expected. Infused saline functions as a "liquid electrode" within the tissue to be ablated and spreads applied RF energy away from the metal electrode to the surrounding tissue. Therefore, both the central

resistive heating rim and peripheral passive heating area are increased, hence a larger lesion can be obtained. When saline is infused, some convective cooling also occurs at the tip. Besides, steaming is retarded by the increased boiling temperature of tissue fluid in which hypertonic saline is added.

As demonstrated in our experiments, the current invention of expandable wet electrode combines the advantages of "wet" electrode and expandable-dry electrodes, yielding an optimized result of RFA. This novel approach may allow to obtain by a single procedure and in one session, a lesion of sufficient size of tumor eradication. In theory, still a novel type of electrode can be made by combining internally cooled mechanism with the present expandable-wet fashion.

The invention there claim the novel application of combining expandable electrodes together with the infusion of a nontoxic conductive solution at the electrode-tissue interface for improved conductivity at the electrode-tissue interface and increased lesion size during RF energy delivery, for example during tissue ablation procedures.

CLAIMS

1. Device for delivering radio-frequence (RF) energy, for example during tissue ablation procedures, comprising a delivery catheter with a distal end and a proximal end and an electrode deployment device positioned at least partially in the delivery catheter including a plurality of retractable electrodes, each electrode having a non-deployed state when positioned within the delivery catheter and a distended deployed state when advanced from the distal end of the delivery catheter defining an ablation volume between the deployed electrodes, said device further comprises wetting means for wetting the proximity of the distal end of the electrode and adjacent tissue with a non-toxic (RF) conductive solution.

2. Device according to claim 1, wherein at least one of the electrodes is straight.

3. Device according to claim 1 or 2, further comprising cooling means for at least cooling the distal end of each electrode.

4. Device according to claim 1, 2 or 3, wherein the electrodes are hollow defining a channel for the wetting solution.

5. Device according to any of the previous claims 1-4, wherein the distal end of the electrode is sharpened.

6. Device according to any of the previous claims 1-5, wherein the device further is provided with cooling means for cooling at least the distal end of the electrodes.

7. Device according to any of the previous claims 1-6, wherein the distal end of the electrode is provided with temperature monitoring means.

8. Guidance element for the guidance of an instrument when introduced and longitudinally displaced in said element for use in for example radio-frequency ablation procedures which guidance element is substanti-

ally formed by an open hollow shaft having a central cilindrical bore.

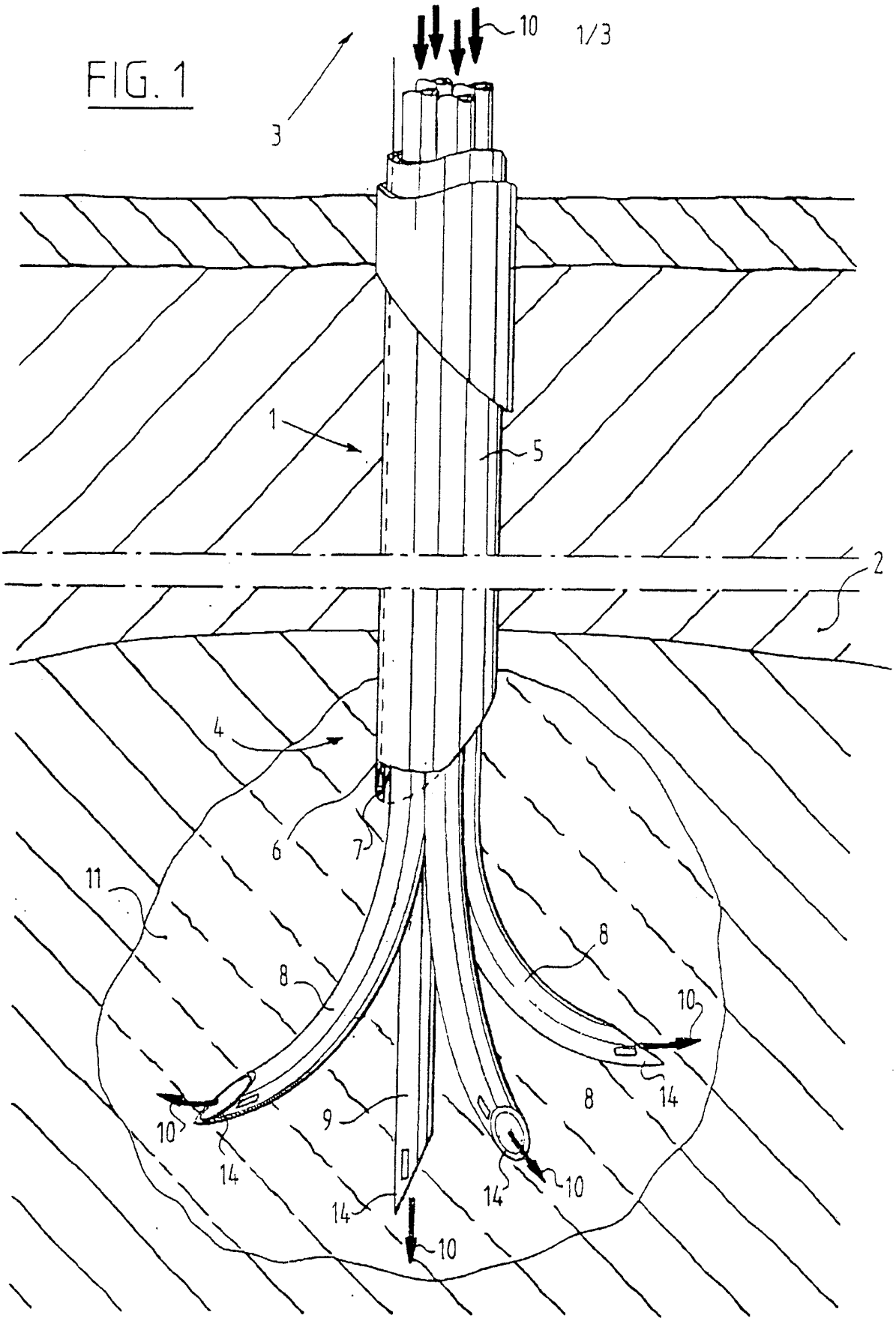
9. Guidance element according to claim 8, wherein said element is chozen from a puncturing needle, a radio-frequency ablation electrode or a biopsy needle.

10. Use of the device as defined in any of the previous claims 1-7 for RF tissue ablation procedures.

11. Process for wetting a radio-frequency energy delivering device as defined in any of the previous claims 1-7 comprising the steps of providing a wetting solution to the proximity of an open distal end of the electrode.

12. Process according to claim 11, further comprising delivering a cooling solution at the distal end of the electrodes by the transport of a cooling solution through an inner channel in said electrodes.

FIG. 1



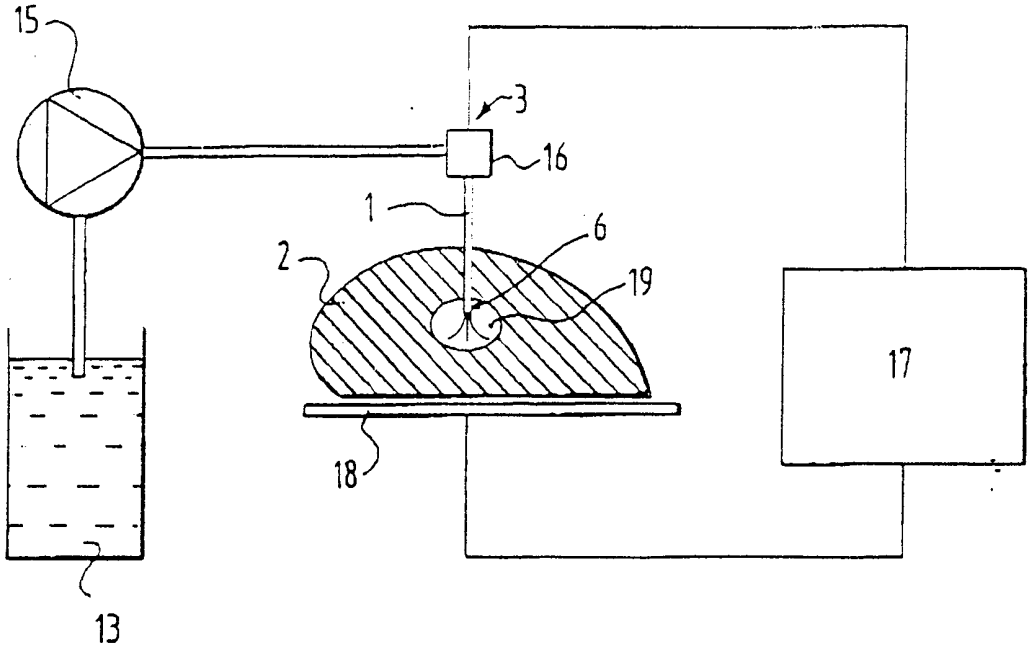


FIG. 2

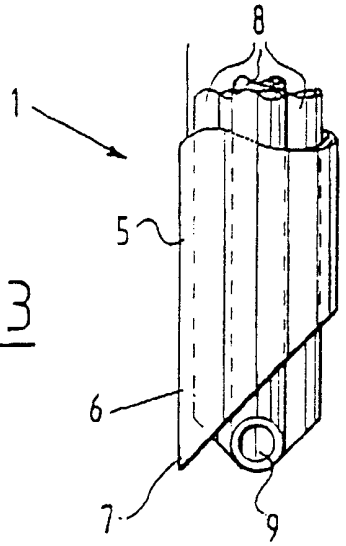


FIG. 3

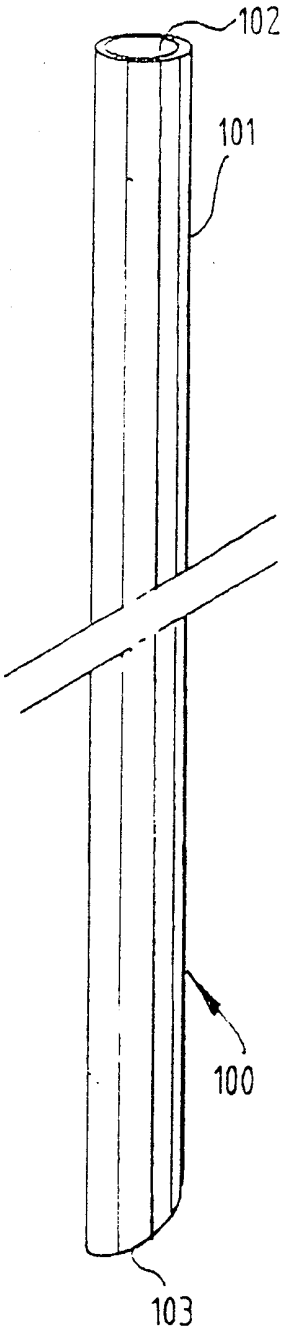


FIG.4A

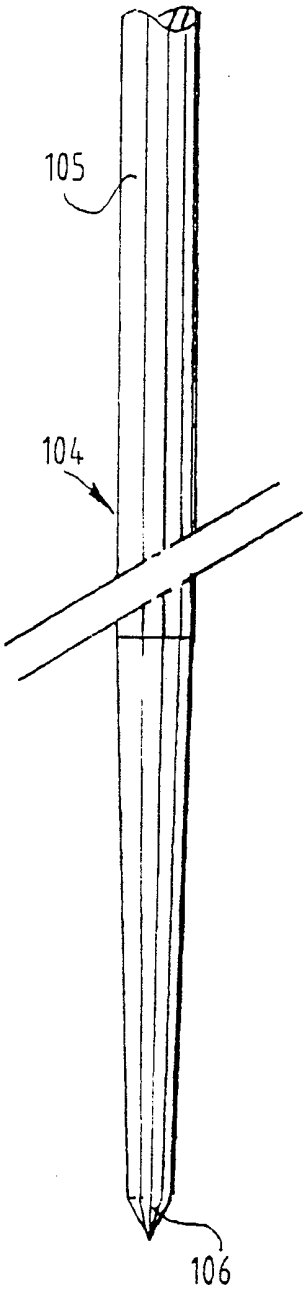


FIG.4B

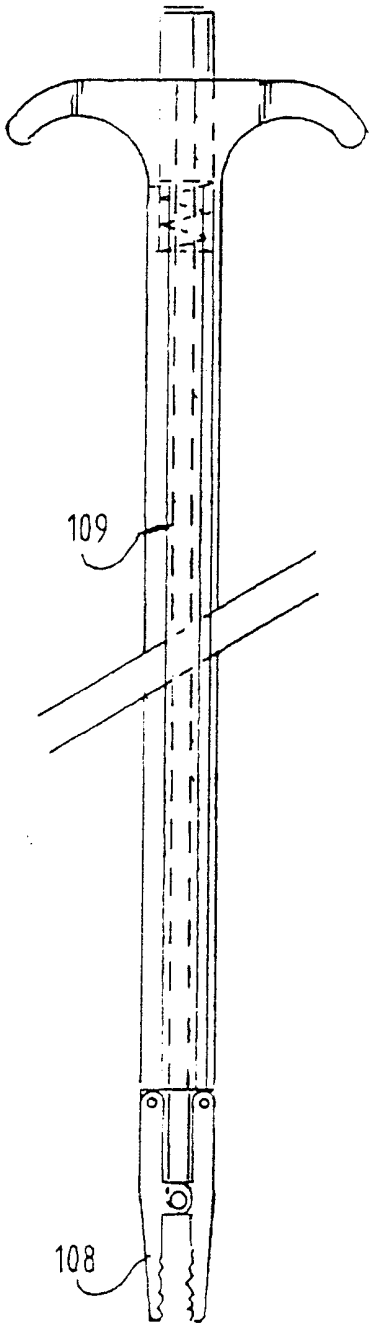


FIG.4C

INTERNATIONAL SEARCH REPORT

Inte onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N1/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TORBEN LORENTZEN: "A Cooled Needle Electrode for Radiofrequency Tissue Ablation : Thermodynamics Aspects of Improved Performance Compared with Coventional Needle Design" ACADEMIC RADIOLOGY, vol. 3, no. 7, 7 March 1996 (1996-03-07), pages 556-563, XP000852585 Herlev, Denmark cited in the application the whole document ---	1-6,11, 12
X	WO 98 03220 A (ARTHROCARE CORP) 29 January 1998 (1998-01-29)	8,9
A	page 27, line 32 -page 31, line 3 page 37, line 13 -page 40, line 10; figures 1-4,21-23 --- -/--	1,3,6-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/BE 99/00107

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S. ROSSI, E. BUSCARINI ET AL.: "Percutaneous Treatment of Small Hepatic Tumors by an Expandable RF Needle Electrode" AMERICAN JOURNAL OF ROENTGENOLOGY, vol. 170, no. 4, April 1998 (1998-04), pages 1015-1022, XP000852550 cited in the application the whole document	1,3,4,8, 11,12
X	US 5 472 441 A (LAX RONALD G ET AL) 5 December 1995 (1995-12-05)	8,9
A	column 6, line 66 -column 11, line 3; figures 1-5,7,10-13	1,2,5
A	YI MIAO, YICHENG NI ET AL.: "Ex Vivo Experiment on Radiofrequency Liver Ablation with Saline Infusion through a Screw-Tip Cannulated Electrode" JOURNAL OF SURGICAL RESEARCH, vol. 71, no. 1, 15 July 1997 (1997-07-15), pages 19-24, XP000852546 cited in the application the whole document	1-3,6,7, 11,12
A	EP 0 115 420 A (KUREHA CHEMICAL IND CO LTD) 8 August 1984 (1984-08-08) page 7, line 19 -page 16, line 1; figures 1,11-16	1-3,6,7, 12
A	WO 95 05781 A (MEDTRONIC INC) 2 March 1995 (1995-03-02) page 3, line 17 -page 8, line 12; figures	1-6,11, 12

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE 99/00107

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.nformation on patent family members

Inte. onal Application No
PCT/BE 99/00107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9803220 A	29-01-1998	US 5843019 A	01-12-1998
		AU 3663597 A	10-02-1998
		EP 0917482 A	26-05-1999
US 5472441 A	05-12-1995	US 5458597 A	17-10-1995
		AU 1051495 A	29-05-1995
		WO 9513113 A	18-05-1995
		US 5536267 A	16-07-1996
		US 5507743 A	16-04-1996
		US 5599345 A	04-02-1997
		US 5599346 A	04-02-1997
		US 5683384 A	04-11-1997
		US 5935123 A	10-08-1999
		US 5928229 A	27-07-1999
EP 0115420 A	08-08-1984	JP 1537856 C	16-01-1990
		JP 59135066 A	03-08-1984
		JP 62048505 B	14-10-1987
		JP 1836226 C	11-04-1994
		JP 4002276 B	17-01-1992
		JP 59135067 A	03-08-1984
		JP 1618818 C	30-09-1991
		JP 2041971 B	20-09-1990
		JP 60119962 A	27-06-1985
		CA 1244889 A,C	15-11-1988
		DE 3468625 A	18-02-1988
		DK 29984 A,B,	25-07-1984
		US 4676258 A	30-06-1987
WO 9505781 A	02-03-1995	US 5431649 A	11-07-1995
		AU 676630 B	13-03-1997
		AU 1427995 A	21-03-1995
		CA 2168860 A	02-03-1995
		DE 69419038 D	15-07-1999
		EP 0774926 A	28-05-1997
		JP 2761440 B	04-06-1998
		JP 9500810 T	28-01-1997
		US 5980516 A	09-11-1999
		US 5807395 A	15-09-1998