FONDAZIONE ISTITUTO ITALIANO DI TECNOLOGIA

A TECHNOLOGY TEASER

FIDUCIAL MARKERS FOR STEREOTACTIC RADIOSURGERY

ISTITUTO ITALIANO DI TECNOLOGIA

Released on June 2016

HEALTH TECHNOLOGIES

Istituto Italiano di Tecnologia – Mission and History

The Foundation is intended to promote Italy's technological development and advanced education, consistent with national policies for scientific and technological development, thus strengthening the national production system.
For this purpose, the Foundation:

- helps and accelerates the development, within the national research system, of scientific and technological skills able to facilitate state of the art technological advancements of the national production system;

- develops innovative methods and know-how, in order to facilitate new high-level practices and positive competitive mechanisms in the field of national research;

- promotes and develops scientific and technological excellence, both directly, through its multi-disciplinary research laboratories, and indirectly, through a wide collaboration with national and international laboratories and research teams;

- carries out advanced training programs as a part of wider multi-disciplinary projects and programs;

- fosters a culture based on sharing and valuing results, to be used in order to improve production and for welfare-related purposes, both internally and in relation to the entire national research system;

- creates technological understanding about components, methods, processes and techniques to be used for the implementation and interconnection of innovative products and services, in strategic areas for the competitiveness of the national production system;

- pools research scientists operating in various research institutes and establishes cooperation agreements with high-level, specialized centers;

- promotes interactions between basic research and applied research facilities, encouraging experimental development;

- spreads transparent, merit-based selection mechanisms for research scientists and projects, in compliance with globally approved and established criteria.

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EXECUTIVE SUMMARY

Nowadays more and more treatments for tumors are available: surgery, radiotherapy and chemotherapy are often combined in order to increase life expectancy and surviving possibilities.
Sometimes these treatments cannot be applied and palliative solutions are necessary. When they can be applied, negative side effects general occur on patient's life.
Stereotactic surgery is getting more and more popular because it generally doesn't have severe side effects and can be used also for inoperable tumors. Evidences of its effectiveness are also increasing.

Fiducial markers are necessary tools for stereotactic surgery of some types of tumors. Researchers at IIT propose a new family of fiducial markers which present evident advantages over existing solutions.

These technologies represent a unique chance for companies active in radiopharma market. IIT assets appear well positioned for an out-licensing strategy, providing the licensee partner with the ability to take care of the late stage development, CE certification, scale-up and production process. The licensee should guarantee a high probability of market success based on consolidated marketing & distribution organization. A typical licensing strategy based on entry fee and subsequent royalties on net sales can be envisaged.

In the following paragraphs an IP outlook and a description of the IIT technology are available. Furthermore, the IIT Business and Financial Analysis Office (BFAO) implemented a market analysis and a competitive analysis highlighting the profiles of the most active industrial players in the sector.

INTELLECTUAL PROPERTY

PCT Application #	PCT/IB2016/051914 – 5th April 2016
Priority Application #	IT 102015000011062 – 7th April 2015
Applicant	Fondazione Istituto Italiano di Tecnologia
Inventors	Gabriele MAIORANO, Elisa MELE, Athanassia ATHANASSIOU, Pier Paolo POMPA
Title	Fiducial marker for use in stereotactic radiosurgery and process of production

Short Description

Composition in the form of shaped device, for use as a fiducial marker in the body, in radiotherapy and/or radiosurgery comprising a core consisting of a colloidal dispersion of metal nanoparticles and/or oxides or metal salts having X-ray-contrast properties, where said nanoparticles are stabilized with surfactants, polymers or capping agents in a liquid vehicle, and a casing that encapsulates the core polymer, said device having a minimum size of not less than 500 microns and a maximum size not greater than 3000 microns.

IIT TECHNOLOGY

Introduction to stereotactic radiosurgery

Technical progress is providing doctors and patients with new tools and treatments in fight against cancer.
Radiotherapy is a common treatment for patients having a tumor; the basic idea is to use ionizing radiations to kill malignant cells. Since locating the tumor is not always an easy operation, radiotherapy is not an accurate treatment and may lead to negative side effects also on healthy cells nearby the tumor. For this reason, radiotherapy has been considered so far a secondary treatment, sometimes palliative, to resort to when surgery is not possible.
Lately IMRT (intensity modulated radiotherapy) and IGRT (image guided radiotherapy) has changed the scenario, enabling the so-called **stereotactic radiosurgery**. IMRT technologies allow to concentrate great amount of ionizing radiations with great precision, in order to preserve healthy cells and tissues. Rapid Arc® and Cyberknife® are well-known devices based on this technology.
These devices require IGRT to increase their effectiveness. IGRT allows to monitor the position of the tumor from different points of views, comparing several pictures in real time, so that the ionizing radiations are well addressed to tumorous site.
As a consequence, stereotactic surgery is far more effective than traditional radiotherapy.

Tumor localization for frameless stereotactic radiosurgery: fiducial markers[1]

Tumor localization is based on the use of the image-guided technique that is referred to as frameless stereotactic radiosurgery. Once the imaging is done and the exact size, shape and location of the tumor is determined, a treatment plan will be specifically designed by a medical physicist in conjunction with the patient's doctors. The medical team determines the size of the area to be targeted by the radiation and the radiation dose, as well as identifying critical structures – such as the spinal cord or vital organs – where radiation should be minimized.
It is necessary to use some anatomical or artificial features (fiducials) to orient the robot to deliver X-ray radiation, since the tumor is never sufficiently well defined (sometimes even visible at all) on the X-ray camera images (Fig.1).

[1] In collaboration with M.C. Frassanito e E. Restini (Mater Dei Hospital, Bari) - Nanoscale, 2016, 8, 18921

Fig. 1 - Gold fiducial markers are generally cylindrical. On the right, the markers in a lung

Fiducial markers are gold seeds (0.8 mm x 5 mm) implanted in and/or around a soft tissue tumor (or within the bony spine) in number of around 6-8 to act as a radiologic landmark, to define the target lesion's position with millimeter precision.

They are typically placed using a CT (computed tomography) or other image-guided transdermal method (Fig.2).

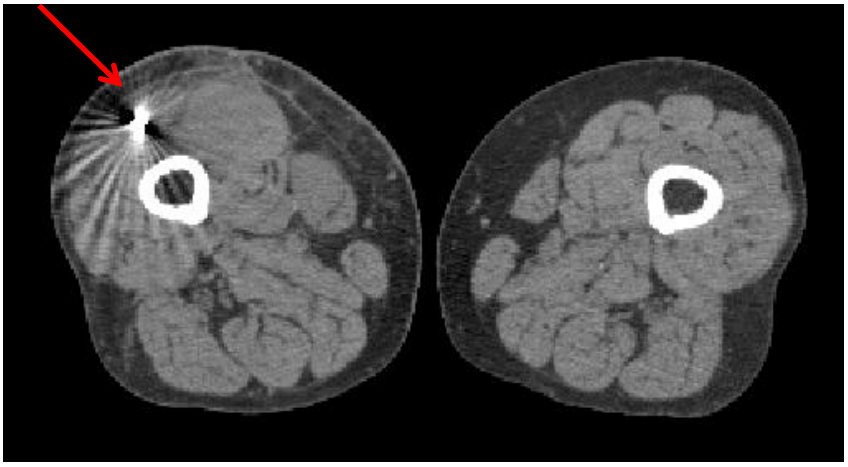


Fig. 2 - Standard gold fiducial marker implanted in leg (HUavr 4600)

The IIT Solution

Istituto Italiano di Tecnologia (IIT) have developed NanoX (Patent Application IT 102015000011062): innovative fiducial markers based on nanostructured gold particles encapsulated in biocompatible polymer that is approved for long-term implantable medical device. These novel fiducial markers can be finely tuned in shape and size (the minimum diameter explored is 0.8 mm) and are suitable for endoscopic placement, thus allowing to reach unexplored body districts by a minimally invasive approach. (Fig.4)

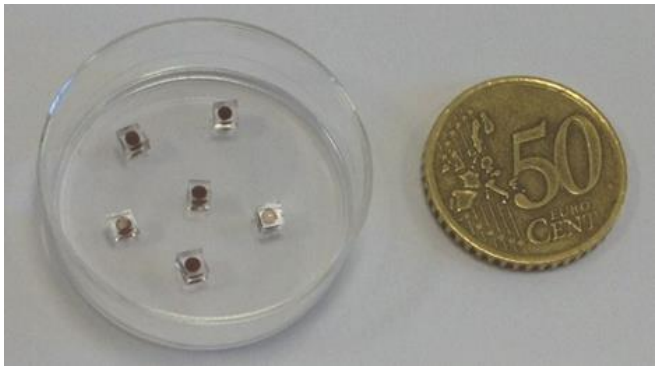
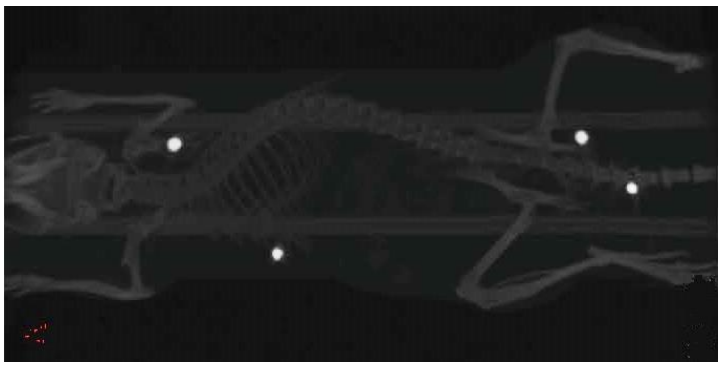


Fig. 4 – IIT fiducials have limited size. On the left, NanoX with a diameter of 1.8 mm

NanoX guarantees an optimal contrast on X-ray images, thanks to the possibility to easily modulate the contrast level (HU) by modulating the nanoparticle concentration (HU from 3000 up to 20000, Fig. 5). Moreover, NanoX fiducial markers are characterized by a drastic reduction of streak artifacts.

Fig. 5 - CT-based images of NanoX with increasing radiodensity (expressed as HU) - Experiments performed in collaboration with M.C. Frassanito e E. Restini (Mater Dei Hospital, Bari) - Nanoscale, 2016, 8, 18921.

The exclusive nanofabrication technology offers **biocompatible** and **extremely stable** fiducial markers. The stability and effectiveness of NanoX were evaluated in vivo by implanting these fiducial markers in mice. CT-based images were acquired for 2 weeks confirming the high performance of these hybrid structures (Fig.6).



Fiducial	Hu
Armpit	16028
Costal	14001
Muscle	15333
Scrotum	13273

Fig. 6 - CT image of a mice 2 weeks later the implant of four NanoX with a diameter of 1.2 mm in different body districts. On the right, the HU values of NanoX, 2 weeks after the implant - Experiments performed in collaboration with M.C. Frassanito e E. Restini (Mater Dei Hospital, Bari) - Nanoscale, 2016, 8, 18921.

The Nanostructure

Recent studies show that nanoparticles are better contrast media than the equivalent macrostructures. However, keeping in place the nanoparticles may represent a technical issue.
The patented nanostructure proposed by IIT has the following components:

1) **Nanoparticles**. Heavy elements, which are more visible to X rays, are suggested. The most common element is gold. The size of the particles is between 1-1000 nm, preferably 50-200 nm.
2) **A capping agent**. It stabilizes the particles.
3) **Solution**. A water solution containing approved hydrophilic compounds.
4) **A polymer**. The polymer covers the nanostructure. It can be natural, synthetic, bioinspired, but if possible approved; it also provides the nanostructures with the required flexibility and elasticity. A drug can be added to the polymer, in order to guarantee a controlled release of the drug in the body. Some examples of polymers are polytetrafluoroethylene, polypropene, polyester, and acrylates, in particular, Poly(2-hydroxyethyl methacrylate).

The size of the complete nanostructure has to be at least 200 µm, but not more than 2000 µm.

In the application IT 102015000011062 a list of particles, solutions and polymers which can be used to reach the goal, is available. The patent also explains a process for the creation of the above-mentioned structure.

Main advantages

Fiducial markers having smaller size guarantee important advantages.

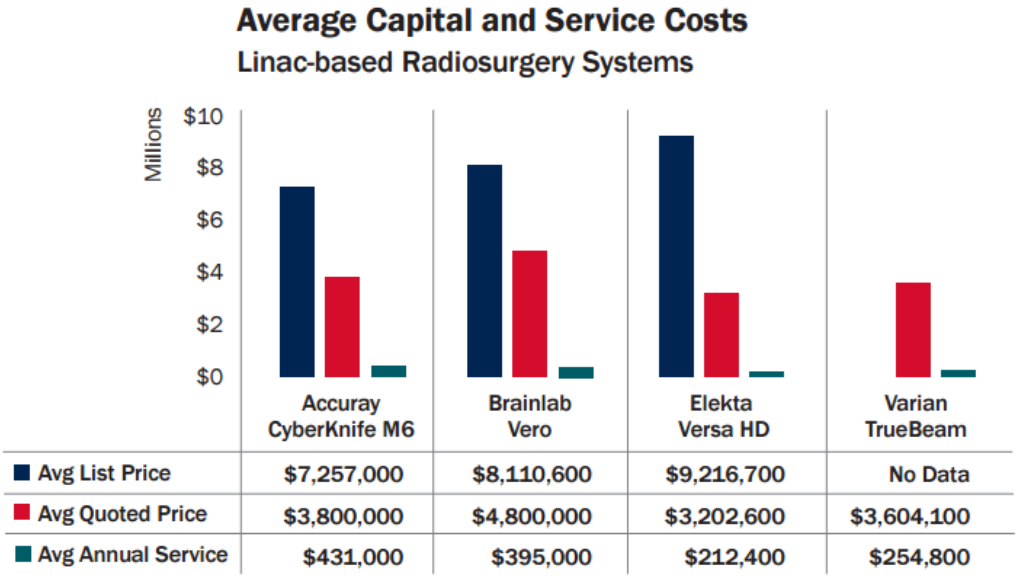
1) **Less invasive for patient**. The fiducial markers can be installed through endoscopy, which is also less risky.
2) **Better contrast media**. According to Hounsfield scale, which describes radiodensity, nanoparticles are far better contrast media. This means that fiducial markers can be visible also with lower doses of ionizing radiations.
3) **Versatility**. Their size makes these markers eligible to be used for more types of tumors, even in parts of the body which can't be reached easily by traditional treatment.
4) **Cost reduction**. They cost far less, since less material is required.

Fiducial markers are necessary tools for IMRT and IGRT technologies. Their spread has to be correlated to the spread of these technologies. This will be examined in depth in next chapters, the market and the competitive analysis.

MARKET ANALYSIS

Market of linear accelerators (linac)

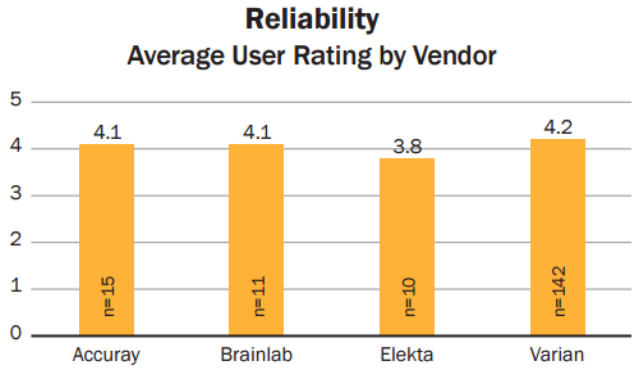
Linear accelerators are the devices used in stereotactic radiosurgery. According to a 2015 survey[1], four vendors are currently considered market leaders: Accuray, Brainlab, Elekta, and Varian.
In the chart below the price for the product and the annual service is shown.



	Accuray CyberKnife M6	Brainlab Vero	Elekta Versa HD	Varian TrueBeam
Avg List Price	$7,257,000	$8,110,600	$9,216,700	No Data
Avg Quoted Price	$3,800,000	$4,800,000	$3,202,600	$3,604,100
Avg Annual Service	$431,000	$395,000	$212,400	$254,800

(Quoted prices may include complementary products bundled with the linac.)

These machines are relatively expensive and represent an important investment for hospitals and other health structures. As a matter of fact, this may slow down their diffusion.



The report also suggests that they are considered equally reliable by the users.

Cyberknife® is available in more than 150 treatment centers in the USA, 30 in Japan, 20 in China, 10 in France and Germany, 8 in Italy and several other around the world. As of December 2010 more than

100,000 patients have been treated worldwide by the CyberKnife System. More than half of those patients were treated with lesions or tumors outside of the brain and head[2].
In 2012 Elekta sold its 3000th linear accelerator[3].
Truebeam by Varian is available in more than 200 treatment centers in the USA and more than 40 in Europe[4].
Looking forward, system upgrades and the replacement of existing equipment will continue to drive market growth for linear accelerators and stereotactic radiosurgery systems as the technology is constantly improving.

Market of fiducial markers

Stereotactic radiosurgery with fiducial markers can be used to treat several types of tumors. Market of fiducial markers can be estimated indirectly through the incidence of most common tumors in population.
Prostate, lung and colorectal tumors are eligible types to be treated via stereotactic radiosurgery with fiducial markers. These tumors are also the most common.

Prostate cancer

Recent studies have shown that stereotactic radiosurgery has and important success rate in the treatment of prostate cancer. The cure rate of conventional radiation in 5 years is between 80 and 90 percent, while stereotactic surgery, according to researchers at UT Southwestern Medical Center, reached a cure rate of 98,6%[5].

An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions, although the cases in less developed country may be underestimated. With an estimated 307,000 deaths in 2012, prostate cancer is the fifth leading cause of death from cancer in men (6.6% of the total men deaths). Mortality is higher in less developed regions than in more developed regions (165,000 and 142,000, respectively)[6].

The picture on the right shows three fiducial markers applied in loco for prostate treatment.

Lung cancer

Lung cancer has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in the less developed regions. The disease remains as the most common cancer in men worldwide (1.2 million, 16.7% of the total)[7].
Stereotactic radiosurgery has revealed to be effective in the treatment of lung cancer, allowing to increase the life expectancy, especially in inoperable cases. A study by the Japan Clinical Oncology Group (JCOG) showed that the overall three-year survival rate for patients treated with stereotactic radiosurgery was 60

percent. Earlier studies on conventional radiation in inoperable patients had shown overall three-year survival rates ranging from 31 to 39 percent[8].

Colorectal cancer

Colorectal cancer is the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) worldwide. Almost 55% of the cases occur in more developed regions. Mortality is lower (694,000 deaths, 8.5% of the total) with more deaths (52%) in the less developed regions of the world, reflecting a poorer survival in these regions[7].

The effectiveness of stereotactic radiosurgery for colorectal cancers is still under evaluation, but recent studies have shown a promising capacity of local control over metastases in liver and lungs[9].

Considerations

Since stereotactic radiosurgery has been introduced lately, the first evidences of its effectiveness, even in combination with other treatments, are still emerging and will more likely emerge in next years.

Moreover, technical progress will allow to reduce the costs for the machinery and will facilitate the spread of these technologies.

The application of fiducial markers is necessary especially for tumors in soft tissues, such as prostate, lung and colorectal cancers, which are also the most common types of tumors. For these reasons, an increase in the demand of fiducial markers in next years has to be expected.

Main sources

[1] https://www.ecri.org/Resources/Whitepapers_and_reports/techIQ_Linear_Accelerator.pdf
[2] http://www.accuray.com
[3] http://www.radpro.eu/news/newsitem92.html
[4] https://www.varian.com/oncology/treatment_locator
[5] https://www.sciencedaily.com/releases/2016/04/160418145458.htm
[6] http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/prostate-cancer-statistics
[7] http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx
[8] http://www.rsna.org/NewsDetail.aspx?id=9297
[9] http://www.tandfonline.com/doi/pdf/10.1080/02841860600904854

COMPETITIVE SCENARIO

Benchmarking

The advantages of IIT fiducial makers over traditional fiducial makers have already been stated: they are less invasive, provide better contrast media, can be used in more situations and cost less.

Moreover, complications during traditional fiducial markers insertion may occur: bleeding, infection, pneumothorax in 33–68% of patients are just few examples. Common fiducial markers may also migrate into the pleural space, the airway, or into the vascular structures.

IIT fiducial markers have several advantages also over innovative fiducial makers containing nanoparticles. The major issues that have to be faced in this type of fiducial markers are the following ones:

1) **Nanoparticles concentration**. Existing solutions don't allow to keep the concentration high enough. Nanoparticles are diluted in matrices which lower the contrast efficiency.
2) **Nanoparticles chemical stability**. Some studies have shown that nanomaterial tends to react to biological tissues nearby, even the healthy ones. Sometimes these fiducial markers can also dissolve, losing efficiency as contrast media and having negative biologic side effects.
3) **Nanostructure morphology.** Traditional nanostructures are generally not suitable for endoscopy.

IIT fiducial markers offer a solution to all these issues, thanks to their specific structure and the choice of materials.

Key players and major companies active in radiopharma market

- AAA (Advanced Accelerator Applications) (Italy, http://www.adacap.com/it/)
- AB Medica (Italy, http://www.abmedica.it/)
- Arplay Medical (France, http://www.arplay.com/)
- Brumola (Italy, http://www.brumola.com/)
- CIVCO Medical Solutions (USA, http://www.civco.com/mmi.htm)
- CP Medical, (USA, http://www.cpmedical.com/)
- Eckert & Ziegler (Germany, http://www.ezag.com/)
- EL.SE (Italy, http://www.el-se.com/it/)
- IBA Dosimetry GmbH (Germany, http://www.iba-dosimetry.com/)
- Medtronic (USA, http://superdimension.com/)
- Naslund Medical AB (Sweden, http://www.fineneedlemarker.com/index.html)
- ONC Solutions (USA, http://www.oncsol.com/)
- Qfix (USA, http://www.qfix.com/)
- QLRAD (Netherlands, http://qlrad.com/)
- SeeDOS (UK, http://www.seedos.co.uk/)
- Tecnologie Avanzate (Italy, http://www.tecnologieavanzate.com/)
- TeamBest (USA, http://www.teambest.com/index.html)
- Tema Sinergie, S.p.A. (Italy, http://www.temasinergie.com/)

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