

PROTON THERAPY

FREQUENTLY ASKED QUESTIONS

Table of contents

1. What is cancer?	2
2. How is cancer treated?	3
3. What is proton therapy?	4
4. What are the clinical benefits of proton therapy?	4
5. What types of tumors require proton therapy?	6
6. How does proton therapy work?	7
7. What is the treatment process in proton therapy?	8
8. How and where can I be treated with proton therapy?	9
9. What is the future of proton therapy?	9
10. What clinical results can be expected from proton therapy?	10
11. Are there side effects?	10
12. When has the first patient been treated with proton therapy?	10
13. Is proton therapy adapted to my case?	10
14. Can proton therapy be combined with other types of cancer treatment?	10
15. How does proton therapy enhance a cancer care program ?	11
16. How many patients can really benefit from PT?	11

ANSWERS TO FREQUENTLY ASKED QUESTIONS

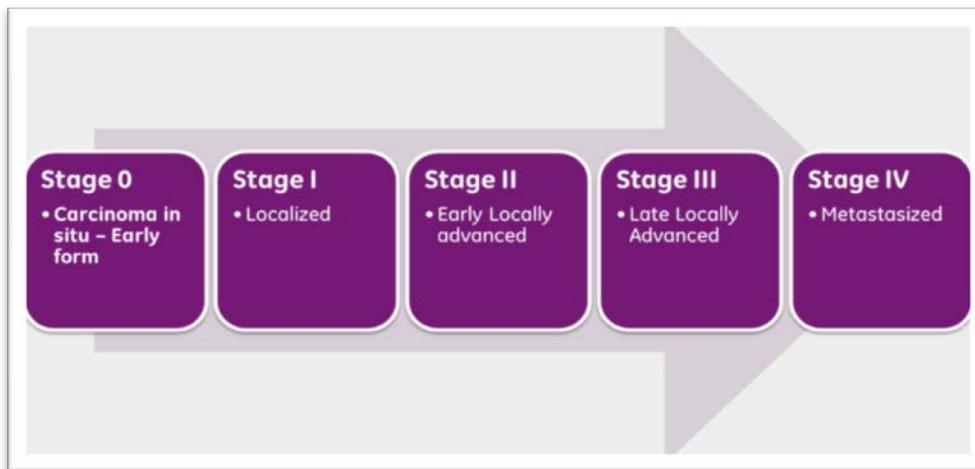
1. What is cancer?

Cancer results from an **abnormal cell proliferation** that ultimately destroys the tissue from which it originates. The cancer cells are all derived from the same initiating cell that has acquired certain properties (independence from cell division signals, etc.) and **divides indefinitely**. As the disease progresses, these cells can migrate and spread to other tissue to form **metastases**. This is why cancer screening should be done as early as possible.

The term "cancer" is a general term for a set of circumstances where the cells adopt a particular abnormal behavior. It is thus not a single well-defined disease, but can result in a **large number of very different conditions**.

The evolution of cancer comprises **four major steps**, determined by the type and size of the tumor, and the involvement of regional lymph nodes and adjacent organs:

- Stage 0: A few cancerous cells appear within healthy tissue.
- Stage 1: The tumor is very localized.
- Stage 2: The nodes near the tumor are invaded by cancerous cells.
- Stage 3: The cancer spreads and reaches the neighboring organs.
- Stage 4: Metastases: organs distant from the initial site are affected.



2. How is cancer treated?

There are three main types of treatments to fight cancer :



Chemotherapy is **used to fight many cancers** and consists in the administration (intravenous or oral) of drugs designed to target cells that develop rapidly, such as cancer cells. However, there are also healthy cells that multiply rapidly in the human body, such as bone marrow stem cells that regenerate blood cells, digestive cells, cells that grow hair, sex cells, etc., which explains the adverse effects of this type of treatment.

There are many different anti-cancer drugs, with their own mode of action and side effects. Chemotherapy is a systemic drug therapy (it has a global effect on the body) and is especially indicated for metastatic cancers.

It serves several different purposes: **permanently cure** the disease, in combination with surgery and/or radiotherapy, **reach long-term remission** allowing for a normal life, or **relieve the symptoms** by reducing the volume of the tumor (palliative chemotherapy).

Surgery is performed when the **tumor is solid and localized**. It consists in **physically extracting** the tumor and involved lymph nodes.

Radiotherapy is the medical use of **ionizing radiation** (also called "beams") to control or kill malignant cells. These beams aim at damaging the DNA of cancer cells, resulting in their death and destroying the tumor.

With surgery, radiation therapy is the most common cancer treatment and can result in net remission on its own. It is generally indicated **after surgery** to remove the last cancer cells and **prevent a relapse**. Hospitalization is not always necessary because the sessions are short and there are fewer side effects than with chemotherapy.

Proton therapy is an advanced form of radiation therapy using a beam of high-energy protons rather than conventional X-rays to irradiate the tumor. This type of treatment can target a higher dose of radiation to the tumor while avoiding healthy surrounding tissue, thus **significantly reducing the risk of secondary radio-induced damage**.

3. What is proton therapy?

Proton therapy is an advanced form of external radiation therapy that uses **high-energy proton beams** rather than traditional X-ray beams to irradiate a tumor. The protons are precisely aimed at cancerous cells, attack their DNA and induce their destruction.

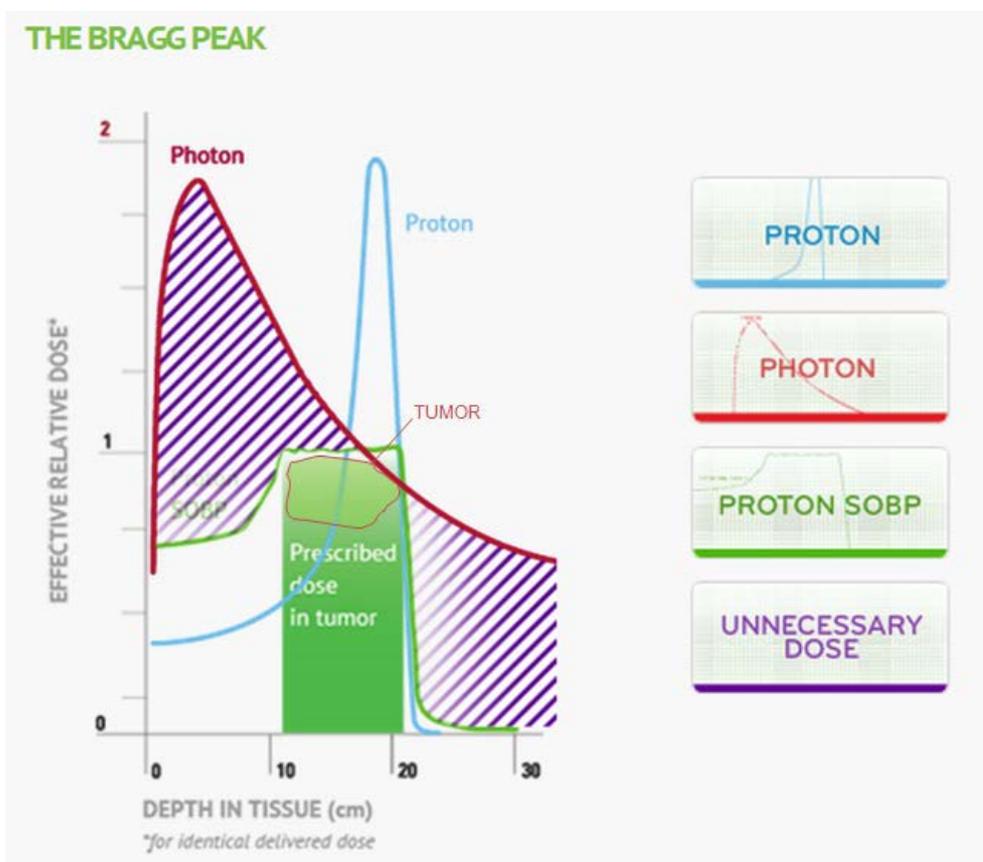
While X-rays are highly penetrating electromagnetic waves that deliver most of their dose before they reach the tumor and tend to affect surrounding healthy tissue, protons deposit most of their energy at a precise and measurable depth that can be perfectly tailored to the tumor location. The absorbed dose of protons increases gradually as it enters the body, suddenly rising to a peak when the protons are slowed down and stopped. This phenomenon is called the **Bragg peak** and allows to significantly reduce the negative effects on healthy tissue.

With this inherent characteristic of protons, it is thus possible to control the radiation dose, to delimit the irradiated region, to identify and to treat the tumor with **unmatched precision, efficiency and safety**.

4. What are the clinical benefits of proton therapy?

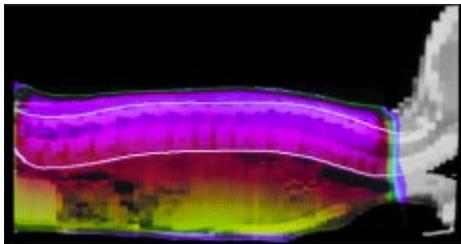
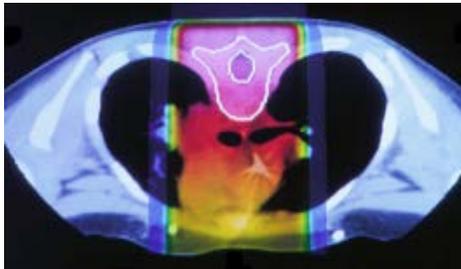
The primary advantage of proton therapy is its **superior dose distribution** to the tumor, with minimal or no exit dose. Due to the unique properties of protons, proton therapy allows to treat tumors with unmatched accuracy, security and efficiency. The administered dose is channeled towards the tumor and **saves healthy surrounding tissue**, thereby **reducing side effects** such as radiation-induced cancers.

Due to their intrinsic physical properties, X-rays used in traditional radiation therapy can damage healthy tissue. They indeed have the particularity to pass through biological matter and tissue, leaving a large dose of radiation before and behind the tumor. Protons, on the other hand, are stopped at a certain point and deposit most of their energy at a **precise and controllable depth** in the patient's body. This particular property is characterized by the **Bragg peak**.

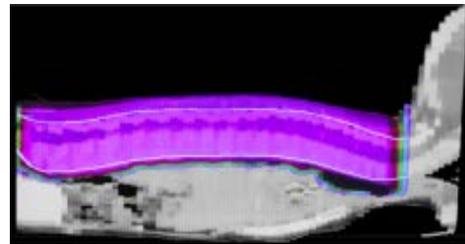
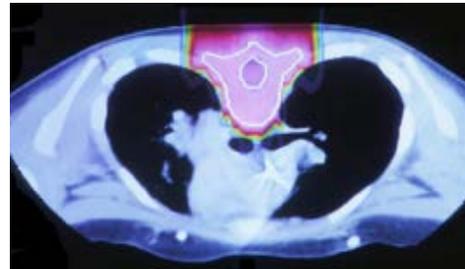


Side effects are thus considerably **reduced** (lower risk of developing secondary cancers, less potential growth abnormalities in children treated, etc...), which implies a **better quality of life** for the patient during and after treatment. PT is also especially appropriate for **cancers with limited treatment options** and those where conventional X-ray radiotherapy presents an unacceptable risk to the patient (eye, brain, spinal cord, prostate and pediatric cancer).

X-rays



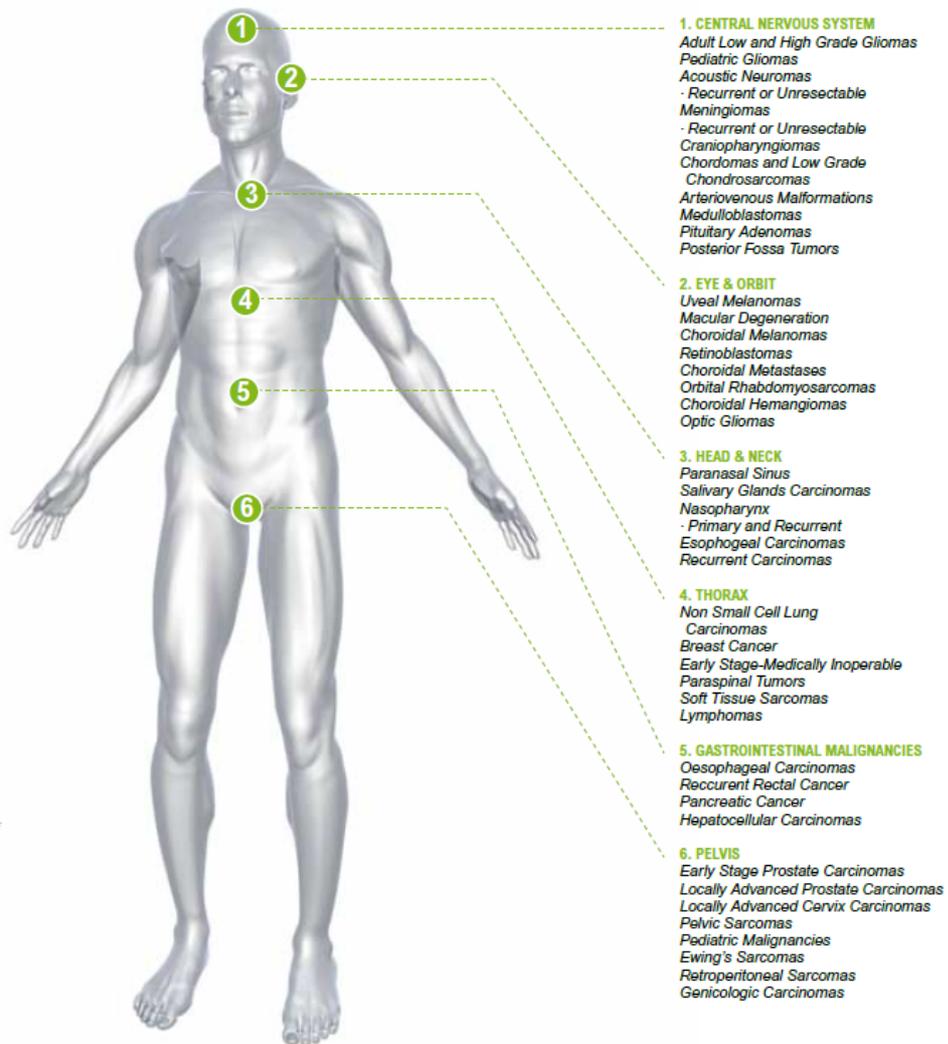
Proton therapy



5. What types of tumors require proton therapy?

Proton therapy is indicated for the treatment of **solid and localized tumors**. It is used today to treat many cancers and is particularly appropriate **when treatment options are limited** (inoperable tumors for example) and when conventional radiotherapy presents unacceptable risks for the patient.

As this type of treatment targets the tumor more precisely than traditional treatments, it is ideal for **tumors close to vital organs** (e.g. central nervous system tumors, ocular and orbital tumors, head and neck tumors, chest tumors, gastrointestinal tumors, pelvic tumors, etc.) and **pediatric tumors**. Indeed, with pediatric malignancies in particular, avoiding even moderate amounts of radiation to normal tissue is vital to prevent cognitive impairments, growth defects, cardiac damage, radiation-induced tumors and other morbidities later in life.



For a general overview of the clinical aspects of proton therapy, refer to the following works:
 - "Proton and charged particle radiotherapy" by Thomas F. Delaney, Hanne M. Kooy
 - "Proton Therapy", Series: Radiation Medicine Rounds Volume 1 Issue 3 by James M. Metz and Charles R. Thomas, Jr

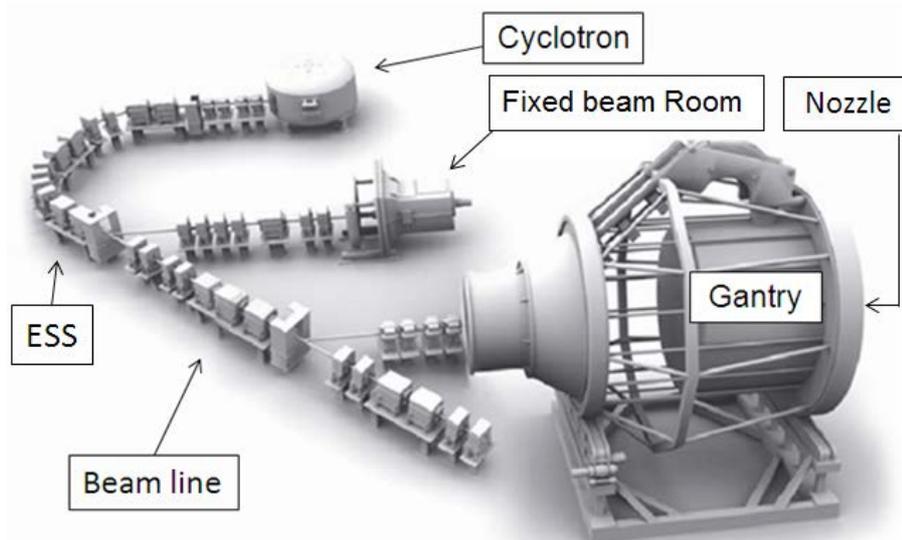
Besides cancer, proton therapy has been effectively used to treat Parkinson's disease, epilepsy, macular degeneration, arteriovenous malformations, severe rheumatologic conditions and seizure disorders.

6. How does proton therapy work?

Proton therapy uses protons to fight cancer by aiming a high-energy ionizing beam at the tumor, ultimately destroying its cells.

In centers equipped by IBA, the world leader in the field, protons come from hydrogen molecules (H_2) and acquire their extremely high speed (up to $2/3$ of the speed of light) in a particle accelerator or "cyclotron". The IBA Energy Selection System (ESS) then gives the protons a definite energy adapted to the treatment plan. Indeed, this amount of energy is equivalent to a particular penetration distance in the patient's body, which is calibrated to correspond to the location of the tumor. The proton beam can also be **adapted to the specific shape of the tumor**, allowing to precisely target the radiation dose and significantly reduce side effects compared to conventional radiation techniques using X-rays, which are highly penetrating electromagnetic waves that deliver most of their dose before they reach the tumor.

The stable and controlled proton beam thus formed is sent to the treatment room through a transport system consisting of magnets called the "beam line", to finally arrive in the "gantry". It is then directed to the cancer patient through a "nozzle" that can target the tumor with **millimeter precision**.



Gantry room with nozzle



Fixed room with nozzle



7. What is the treatment process in proton therapy?

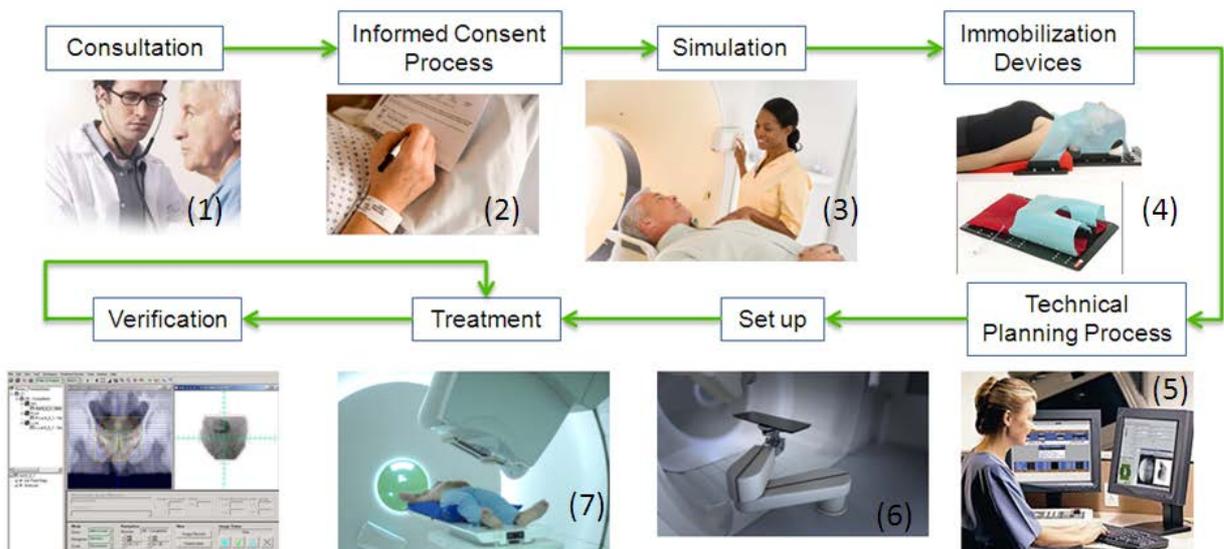
When cancer is suspected, your **general practitioner** (1) prescribes a series of tests (blood tests, CT scan, biopsy,...) to confirm or rule out the disease. If cancer is diagnosed, the doctor will refer the patient to an oncologist to discuss treatment options.

If proton therapy proves to be the treatment of choice and if the patient agrees to be treated this way (2), he will have to go to a **proton therapy center** to perform a **simulation** (3). Thanks to diagnostic images, this simulation allows the hospital team to identify the targeted tumor and the areas through which the proton beam can be directed into the body to cause **minimal side effects**.

To ensure accurate beam delivery, the treatment room is equipped with patient **positioning and immobilization devices** (4,) developed for each patient in order to minimize their movements during future radiation sessions.

Once the treatment plan is completed (5) (after about a week), the patient goes to the proton therapy center where he will be treated (7) (fraction) after being placed in the same position (6) as during the simulation. The number of fractions varies between 5 and 40 depending on the type of tumor.

These fractions are repeated, usually **once a day, five days a week**. The total treatment duration depends on the cancer but usually lasts a few weeks.



8. How and where can I be treated with proton therapy?

To access this type of treatment, the first step is to **discuss proton therapy with your doctor** and share the information you have gathered with him, as oncology covers a wide range of specialties and treatments, of which doctors do not always know all the details. Then, the second essential step is to **contact one of the centers** that offer proton therapy treatment: they will determine whether it is the most appropriate treatment for you and if they still have availabilities. If necessary, the center will contact social security and the patient's insurance, as health care is organized in a local legal framework that can influence access to certain treatment modalities or reimbursement by insurance funds.

Here is a list of proton therapy centers that are used to accommodate patients from around the world: <http://www.proton-therapy-today.com/where-to-get-pt/>.

With nearly 30 years of experience and unparalleled expertise, IBA, the market leader, installed most clinical proton therapy centers in the world and more than 50% of clinical treatment rooms with proton market.

9. What is the future of proton therapy?

Proton therapy is facing different **challenges**. Its intrinsic properties give it pride of place in the fight against cancer but require at the same time cutting edge technology that reduces its accessibility. IBA, the world leader in this field, wants to address these challenges by facilitating access to this technology while providing value-added solutions to meet clinical needs and to demonstrate and promote the sustainable incremental clinical benefits of proton therapy.

There are over **100 proton therapy centers** in the world, mainly in Europe, the USA and Asia, which attract patients from all continents. More and more cancer patients are treated with proton therapy but many of them who could potentially benefit from it are denied access because the installation of these centers requires **significant investments** (it costs from \$25 million to \$125 million to build and equip a proton therapy center).

That is why **IBA** is committed to making proton therapy **more accessible** to healthcare systems and to patients. In this context, IBA has designed the Proteus®ONE, a smaller and more affordable system than other existing products on the market. This system consisting of a single treatment room significantly reduces the cost, space and installation time needed for the construction of the center, thus facilitating access to proton therapy for more people.

This new and more economic system delivers the latest advance in proton therapy, **Intensity Modulated Proton Therapy (IMPT)**. IMPT combines the precise dose delivery of **Pencil Beam Scanning (PBS)**, a millimeter beam directed through the target volume one layer at a time to "paint" the precise form of the tumor, with the dimensionally accurate imaging of **3D Cone Beam Computed Tomography (CBCT)**. This enables physicians to control the intensity and spatial distribution of the dose to the millimeter in order to adapt to the shape and heterogeneity of the tumor while preserving healthy tissue.

Inspired by everyday clinical practice, Proteus®ONE combines powerful clinical capabilities and a patient-centered design, developed in collaboration with Philips Healthcare to foster a soothing and comfortable patient environment while helping the medical staff work more efficiently.

10. What clinical results can be expected from proton therapy?

From a physical point of view, the nature of protons confers numerous advantages to proton therapy compared to conventional radiotherapy. Indeed, protons release their maximal energy in a precisely controlled area, a phenomenon known as the "**Bragg peak**". The proton beam effectively releases its energy inside the tumor and spares the surrounding healthy tissue. On the contrary, traditional X-rays release a greater radiation dose in healthy tissue before and behind the tumor. Proton therapy thus significantly **reduces the radiation dose** and potential resulting side effects.

In clinical terms, proton therapy has already proven its worth, and many scientific articles and other large clinical studies demonstrate that this treatment modality presents real therapeutic benefits, with **good local control, improved survival, less acute toxicity and fewer radiation-induced cancers** than with conventional radiotherapy. Proton therapy has particularly won fame in the treatment of certain types of **complex cancers** such as brain tumors and pediatric malignancies.

Finally, proton therapy **improves the quality of life** during and after treatment, which can be accounted for by more than 100,000 patients treated in different centers in Asia, Europe and the United States.

Download the Selected Bibliography of Scientific Articles here:

<http://www.iba-protontherapy.com/sites/default/files/pt/media%20center/PTReferences-list.pdf>

11. Are there side effects?

Side effects depend on the patient's age, health and medical history. Some patients develop **minor side effects** such as fatigue, skin irritation or slight hair loss. In any case, since the radiation dose affecting healthy tissue is less important than with conventional radiation therapy, side effects will also be reduced.

12. When has the first patient been treated with proton therapy?

Protons have shown their favorable qualities in the treatment of cancer **since the 1950s**. In 1946, Robert Wilson described the ability of protons to release their energy more accurately and intensely, and suggested its use in clinical radiation. The first treatments using protons or helium atoms were performed at the University of California at Berkeley in the U.S. in 1955, the University of Uppsala in Sweden in 1957, Massachusetts General Hospital in the U.S. in 1961, the Physics Research Institute at Dubna in Russia in 1964 and the Institute for Theoretical and Experimental Physics in Moscow, Russia in 1969.

13. Is proton therapy adapted to my case?

This question **should be answered by your doctor**. Each case is unique, and only he will be able to identify the most appropriate treatment for your diagnosis. More information is collected by international organizations and can be found on sites like oncolink.com for example. Patients are encouraged to learn as much as possible about their options and the various treatments available, and discuss it at length with their doctor.

14. Can proton therapy be combined with other types of cancer treatment?

Yes, this is what happens in most cases: depending on the situation, proton therapy can be combined with conventional radiotherapy, chemotherapy and/or surgery.

15. How does proton therapy enhance a cancer care program ?

Proton therapy is the **perfect add-on to advance a cancer care program** and put it on the cutting edge of radiation therapy. The clinical efficiency of PT offers optimized tumor control and lowers the integral dose while preserving the quality of life of patients during and after treatment. It also enhances the continuum of care at the center while boosting its research capabilities.

With proton therapy, clinicians have the capacity to expand their practice and address cases that would be too complex or present too much toxicity with X-rays. Thus the **potential for enhancing care** is tremendous, as proton therapy can benefit to indications that are not suitable for conventional radiation therapy, tumors that need radio-sensitizing chemotherapies or in case of retreatment.

The physical properties of proton therapy give clinical teams the huge opportunity to advance treatment planning, enhance toxicity management and decrease integral dose while increasing the quality of treatment.

Moreover, PT offers an opportunity to **reduce overall cancer treatment costs** for the society by reducing overall long-term side-effects related costs.

Finally, PT alone or combined with other treatment modalities gives patients the opportunity to fight cancer and live a normal life.

16. How many patients can really benefit from PT?

One in three people will suffer from cancer during his lifetime, and a large proportion of them will develop more than one cancer. The vast majority of these patients will receive radiation therapy at some point during their treatment.

The **key indications of PT represent up to 30%** of all cancers treated in conventional radiation therapy. Thanks to its precise dose delivery, PT reduces by 50 to 80% the risk of radiation-induced secondary cancers, and its lower integral dose allows retreatment in case of secondary cancers or cancer resurgence. However, despite this high potential, very few patients today are treated with PT.

The example of the Netherlands:

The Dutch National Health Council recently estimated that in 2015, about 20% of all cancer patients in the country would be able benefit from PT, and concluded that the clinical introduction of PT would require special attention by the Netherlands health care system in the near future. "Proton radiotherapy [...] promises to bring certain advantages over conventional radiotherapy," the report stated. "Its superior physical properties [...] offer the possibility of a better and safer radiation technique for selected indications. [...] This may lead to a reduction of side effects, and/or increased local tumor control, but without an accompanying increase in late normal tissue or organ toxicity. In addition, it may result in reduced risk of secondary malignancies."

The report envisions a gradual adoption of the clinical use of PT in the Netherlands from 1% of all radiation therapy patients to about 20% over the next 20 years. The standard indications for the use of PT include intraocular tumors, chordomas & chondrosarcomas and pediatric malignancies. The next step will be to use PT where a better local control is needed, e.g. intracranial, urologic (prostate & bladder) and lung (NSCLC) cancers among others, which represent 3% of RT patients. PT also offers a real opportunity for retreatment of recurring cancers.

As time passes and evidence builds, clinicians and researchers will be able to demonstrate that PT offers reduced side effects in a number of cancer indications. It concerns most of the above indications as well as breast, gynecological, and gastro-intestinal (esophagus, gastric, rectal, pancreas) cancers as well as lymphomas and sarcomas. It represents 12% of RT patients.

PT really represents an opportunity in oncology. On top of reducing the risk of secondary cancers, the full potential of proton therapy lies in the reduction of side effects to enhance the quality of life of patients during and after treatment.