Medical Data and Financial Context of Carbon Ion Therapy

Updated June 2013

Abstract

Carbon ion therapy is an innovative method of radiotherapy that uses a beam of carbon ions produced by a high-technology device called a synchrotron. This technique is part of the ***continuing progress*** made in radiotherapy in recent decades, continually increasing the difference between the radiation doses to the target and to healthy tissue. Carbon ion therapy combines two advances: a very accurate, focused particle beam (as with proton therapy) and an increased efficacy (as with neutron therapy), particularly at the targeted tumour. ***Carbon ion therapy provides effective treatment for inoperable and highly radioresistant tumours, for which there are currently no good treatment solutions.***

Because the eligible tumours are rare and since there are very few carbon ion therapy facilities – as was initially the case with proton therapy – traditional randomised comparative trials have not yet been possible or justified. Thus, ***a very detailed study of outcomes*** compared with the latest developments in radiotherapy has had to be performed, in order to define the scope of application of carbon ion therapy. This was done by European experts as part of the ENLIGHT project, and then in more detail as part of the ETOILE initiative between 2002 and 2010[1]. As a result of this study two groups of indications were defined: priority indications, known as **consolidated** indications (approximately one thousand cases), and **prospective** indications that include more cases (several thousand). ***It is very important to distinguish between these two types of indications when discussing medical evidence, financial issues and the outlook for the future of the technique.***

The priority indications are ***tumours of the salivary glands, paranasal sinuses, adenoid cystic carcinomas, mucosal melanomas, chordomas of the base of the skull, unresectable or partially resected sarcomas and chondrosarcomas, unresectable local recurrences of rectal cancers and single large hepatocellular carcinomas.***

The analysis of the current status of carbon ion therapy provided in this paper principally covers its **priority, or consolidated, indications**. For some of these indications (chordomas and local recurrences of rectal cancers), therapeutic benefit has already been studied. The results of these studies are convincing and reassuring, showing ***zero or even beneficial impact on health care costs resulting from avoided expenditure, for an average treatment cost of approximately €35,000 per patient*** *(figure for 2012).* In view of the observed differences in local control and survival rates, which can be more than ***20–25% in favour of carbon ion therapy***, systematic conduct of phase III randomised comparative trials would raise an ethical question, in addition to the issue of feasibility when the technique is still emerging.

Discussion about the place and form of comparative clinical trials of radiotherapy therefore falls within the scope of this assessment. According to the 2013 White Paper issued by the SFRO, "phase III randomised trials cannot be the only method of evaluating the therapeutic progress in oncology, particularly in radiotherapy. Other methods must be developed and promoted."***These methods must be suited to the aims pursued***. They may be phase II trials, randomised or otherwise, cohort studies or very long-term follow-up observational studies. The methodology recommendations made in the White Paper do, therefore, apply to carbon ion therapy.

Concerning the other indications, prospective and exceptional indications, they can be studied in prospective randomised clinical trials and observational studies respectively.

[1] Study files and summaries of expert discussions can be consulted at www.centre-etoile.org.

The medical data presented in this document are based on ***various publications*** on phase I/II trials, advanced phase II trials evaluating treatment efficacy, long-term observational studies and cohort studies. They show carbon ion therapy to be 20–25% superior and well tolerated, with low toxicity and a radiation-induced cancer rate of almost zero. In addition, publication of very promising results is beginning in Japan on prospective indications, such as uterine sarcomas, lung cancers and resectable pancreatic cancers, for which the five-year recurrence-free survival rate is 42% (double of the best current results), with no serious adverse effects observed.

A cost of approximately €35,000 (figure for 2012) for carbon ion therapy for one patient seems a reasonable estimate for France, as the ETOILE Centre will be funded mainly by borrowing. This cost would place France at the international standard hospital cost level for carbon ion therapy and would guarantee it international standing in this type of treatment. It also matches the average cost of hospital cancer treatment in France, which arithmetically is a very average cost, even modest, far from the extremely high costs of many other novel anticancer treatments.

Pioneering American studies up to 1993, and the resumption of hadron therapy involving ions in Japan in 1994 and in Europe in 1998, have provided unambiguous proof of the therapeutic efficacy and excellent tolerability of carbon ion therapy, with more than 10,000 patients treated to date in six different health facilities. ***Carbon ion therapy can now be described as an active, reliable, well-tolerated anti-tumour treatment for the main indications explored, and is probably cost-effective for the indications defined as consolidated.***

Glossary

CNAM: National Public Health Insurance in France

CNAO: The National Centre of Hadrontherapy Oncology, a carbontherapy facility in Pavia, Italy

GSI: *Gesellschaft für Schwerionenforschung* (Society for Heavy Ion Research), a fundamental and applied physics research centre in Darmstadt, Germany

HIT: Heidelberg Ion-Beam Therapy Center, a university hadron therapy facility at the University Hospital of Heidelberg, Germany

IMRT: Intensity-modulated radiation therapy

NIRS: National Institute of Radiological Sciences, a national centre for research and development of medical applications of ionising radiations in Chiba, Japan

SFRO: *Société française de Radiothérapie Oncologique* (French Society of Radiation Oncology)

ULICE: Union of Light Ions Centres in Europe

VMAT: Volumetric modulated arc therapy, the most advanced type of IMRT.

Contents

I. Preliminary Work in the *Hadronthérapie France* Project (2002–2010)

Hadron therapy has developed very slowly. From its inception, it has mostly been used to target rare tumours that are very difficult to treat. Also, although it is no longer in its exploratory stage, the first randomised comparative trials (known as phase III trials) of hadrontherapy are still ongoing and their results have not yet been published. Although the very principle of phase III trials in this particular area is questionable (see chapter I.2, page 11), this unusual situation complicates all attempts to develop objective rationals aimed at identifying indications, analysing epidemiology and evaluating the need for care.

To overcome this difficulty, physicians involved in the development of hadrontherapy in France, both proton and carbon ion therapy, formed an original body, always mindful of objectivity and rigour. This group is named **Hadronthérapie France**[2] and includes more than 100 physicians. They undertook this work between 2002 and 2010. The work and its conclusions are described in this initial chapter.

Particle Radiotherapy, or Hadrontherapy

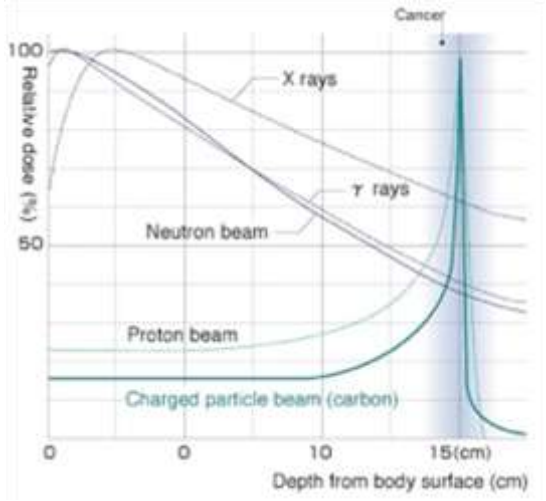


Figure 1: Comparison of ballistic accuracy

Hadrontherapy involving carbon ions (known as carbon ion radiotherapy or carbon ion therapy) uses radiation consisting of carbon atom nuclei accelerated at very high energy levels. This radiation possesses two remarkable properties: very high ballistic accuracy (Figure 1) and tumour destruction power two to three times higher than that of other types of radiations (Figure 2) currently used in radiotherapy (X-rays, electrons and even protons). This means that carbon ion therapy combines the ballistic advantages of protons and the radiobiological advantages of neutrons (which are no longer used in France since 2007).

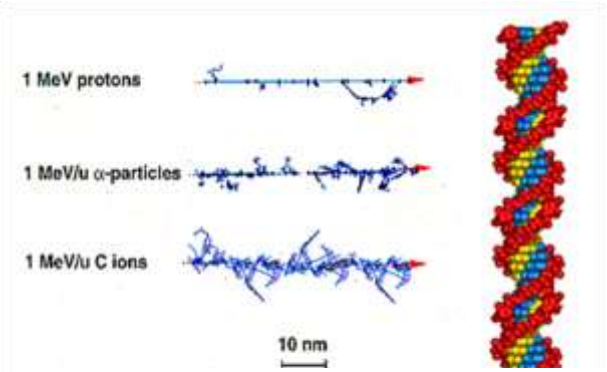


Figure 2: Ionisation density of particles used for therapy compared to the size of DNA

thérapeutiques en comparaison de la taille de l'ADN

Carbon ion therapy is essentially intended for the treatment of ***a specific, limited group of tumours***: inoperable or only partially resectable tumours that are particularly radioresistant and located among radiosensitive healthy tissue. These conditions limit the efficacy of conventional radiotherapy, including conformal intensity-modulated photon therapy and proton therapy, and they rule out the use of neutron therapy, which is much too toxic. Advanced photon therapies such as dynamic arc therapy, tomotherapy and CyberKnife lose their ballistic properties when the average diameter of the target is more than 5–6 cm.

Hadrontherapy has already been used in these tumours for many years. The use of ions and neutrons began in the 1950s in the USA. They required particle accelerators that were then available only in nuclear physics research facilities far away from university care facilities. Now, at the beginning of the 21st century, these treatments have irrefutably been shown to be feasible. Nevertheless, because their

[2] The list of physicians who took part in this work is provided in the appendix to this document.

application remains limited it has not yet been possible to provide statistical validation of them using the standard concepts of evidence-based medicine developed in the world of pharmaceuticals. The indications for which clinical benefit would be greatest must therefore be identified by other means.

Candidate tumours are in fact rather rare, and very varied in terms of their nature and location. Nevertheless, they have been treated using innovative treatments such as neutron therapy, which was a recommended treatment for some sarcomas and some salivary gland tumours until the emergence of carbon ion therapy[3]. Thanks to its ballistic accuracy, carbon ion therapy does not harm healthy tissue to the same extend and can be used in a much higher number of tumours. The group assessment that worked in France to define SORs (Standards, Options and Recommendations; see http://www.sor-cancer.fr/) has already shown an interest in hadrontherapy in at least two areas, issuing clear recommendations for sarcomas in 2006[4] and salivary gland tumours in 2008[5]. The following conclusions can be highlighted in particular, for example:

***SOR: Salivary Glands, 2008:* "Given the recent closure of the Orléans Neutron Therapy Unit, experts have decided to alter the 2003 recommendations by substituting hadrontherapy (using carbon ions or protrons) for neutron therapy when this is feasible in the event of macroscopic residual tumour."**

***SOR: Sarcomas, 2006:* "In clinical practice radiotherapy alone is indicated only for patients with an inoperable tumour or who refuse all other treatment. It is therefore rarely indicated, and its indication must be discussed at a multidisciplinary meeting. Some of these patients might be good candidates for neutron therapy or charged particle beam therapy (using protons or carbon ions)."**

Thanks to technological and medical progress since the late 1990s, health facilities devoted to carbon ion therapy have been established and the use of these treatments on a larger scale for radioresistant tumours has been resumed. To date (as of 2013) the vast majority of this experience has been gained in Japan, where more than 10,000 patients have been treated, but some has also been gained in Europe: around 1,450 patients have been treated in Germany. Several dedicated facilities are under construction in Europe and China, and more in Japan, in addition to plans elsewhere in the World (Asia, the Middle East, Australia, China, Europe, the USA, South Africa).

The French ETOILE Project

France has developed its own project for a carbon ion therapy facility: the ETOILE Centre (www.centre-etoile.org). This is part of the goals of the two Cancer Plans[6]. The decision to establish it was first announced by the French Health Ministry on May12th, 2005: *"Philippe Douste-Blazy, Minister for Solidarity, Health and the Family, and François d'Aubert, Minister for Research, have decided to create a national hadron therapy research centre for anti-cancer treatment. The site in Lyon, close to the CLARA Cancer Research Resource Centre, has been selected for the first facility…"* A first public-private partnership call for tender was then launched following a letter from Xavier Bertrand in February 2007, abandoned in 2010 when finally a real roadmap was provided by a letter from Roselyne Bachelot-Narquin, Minister of Health, dated October 1st, 2010. This letter stated that the State support would

[3] Neutron therapy at Orléans was halted in summer 2007. Orléans was the only operational facility in France. There are two or three facilities remaining in Europe (in Germany and the UK).

[4] http://www.sor-cancer.fr/index.php?tg=fileman&idx=get&inl=1&id=2&gr=Y&path=Peau+et+tissu+de+soutien%2Fsarcome%2Fsarcome+des+tissus+mous&file=Rapport+int%E9gral+2006.pdf

[5] http://www.sor-cancer.fr/index.php?tg=fileman&idx=get&inl=1&id=2&gr=Y&path=Voies+aerodigestives+superieures%2Fcancer+des+glandes+salivaires&file=RPC+SOR-MAJ+2008+glandes+salivaires_revuSR100408.pdf

[6] Step 70 of Cancer Plan 1, Step 21.5 of Cancer Plan 2.

depend on three conditions[7] being met, and they were met by the first quarter of 2012. Two construction firms' bids were then received in mid-July 2012; only one of these complied with the specifications of the tender, however it required too much funding. Negotiations to obtain more favourable conditions began in late 2012 and are due to end hopefully in fall 2013 with a State decision to create a public medical institution for ETOILE making possible the signature of a construction contract in late 2013. This would enable the ETOILE Centre to open in 2018.

The maximum capacity of the ETOILE Centre will be approximately 2,000 patients receiving carbon ion therapy per year. This treatment capacity, which is high for this type of technology, will be sufficient to treat all French patients requiring carbon ion therapy for more than 10 years. Methodological study of the indications of carbon ion therapy has been an important part of the project, in order to model the facility and to complement proton therapy already provided in France for 20 years.

I.1. Methods Used for Comparative Literature Analysis

Hadronthérapie France's study of the indications of carbon ion therapy as part of the ETOILE project

In 2002 the sponsors of the ETOILE project decided to develop a brand-new study and independent assessment procedure for the indications of carbon ion therapy. The procedure was coordinated by the medical team, with the support of the professional team of Prof Jean-Pierre Boissel and Prof Alain Leizorovicz of the Laennec medical school in Lyon, France, which is well-known for clinical trial methodology and evaluation. The overall procedure is shown in Figure 3 below. It involved many physicians from all over France and Europe.[2] At the same time the ETOILE team also took part in similar European projects for the ENLIGHT consortium.

A three-stage procedure: screening, analysis, assessment (Figure 3)

Screening represents needs analysis. Between 2002 and 2003, seven groups of multidisciplinary specialist took the general characteristics of a *locoregionally-progressing radioresistant tumour* as their starting-point and exhaustively reviewed local failures in oncology. This resulted in a preliminary list of 92 ***"potential" indications***.

Analysis consisted of establishing the latest developments for the main groups of potential indications through methodical, exhaustive, critical analysis of the literature, for both conventional treatments and hadrontherapy wherever possible. The reports of these analyses/summaries of the literature are very long documents and can be downloaded from the professional domain of the website of the ETOILE Centre (www.centre-etoile.org). This work reveals the baseline for any improvement in outcomes. In parallel to these analyses, epidemiological studies were conducted in France in order to estimate the incidence of these ***"potential" indications***. An other study was conducted at the same time, in Austria, and drew similar conclusions. In 2004 (Baron et al, Radiother Oncol 2004; 73 Suppl 2: S15–7; Mayer et al, ibid.: S24–8) these studies were used to estimate that the ***potential indications*** of carbon ion therapy accounted for 5–6% of indications of radiotherapy, or approximately 8,000 patients of the 160,000 treated in France every year.

Assessment by disease domain was performed by multidisciplinary groups of experts who were independent of the ETOILE project, all established specialists in the diseases under study.[5] The procedure consisted of submitting the analysis/summary of the literature to the experts and then holding a face-to-face discussion session for them to address the following questions for each indication:

[7] These three conditions were to relaunch a call for tenders for construction, to organise a study enabling French patients to access carbon ion therapy in collaboration with Germany and to obtain scientific validation via France's *Programme d'Investissements d'Avenir* (Future Investment Programme).

i) the validity and consensus on the latest developments in the standard treatments; ii) hadron therapy's potential for these diseases; iii) a precise definition of the indications to maintain; iv) the expected benefit over standard treatments; v) the level of evidence that could be expected and relative priority of the indications. This procedure consistently took account of experience of proton therapy, and the experts' conclusions take into account the place and treatment capacities of proton therapy. Between 2004 and 2010 ten groups of experts met in this way, usually at Paris's Institut-Curie, to analyse the following, in turn:

i) **Head and neck adenocarcinomas**
ii) **Sarcomas**
iii) **High-grade gliomas**
iv) **Thoracic tumours**
v) **Prostate tumours**
vi) **Tumours of the digestive tract**
vii) **Epidermoid carcinoma of the upper respiratory and digestive tracts**
viii) **Paediatric non-neurological solid tumours**
ix) **Extremely rare tumours**
x) **Paediatric neurological tumours**

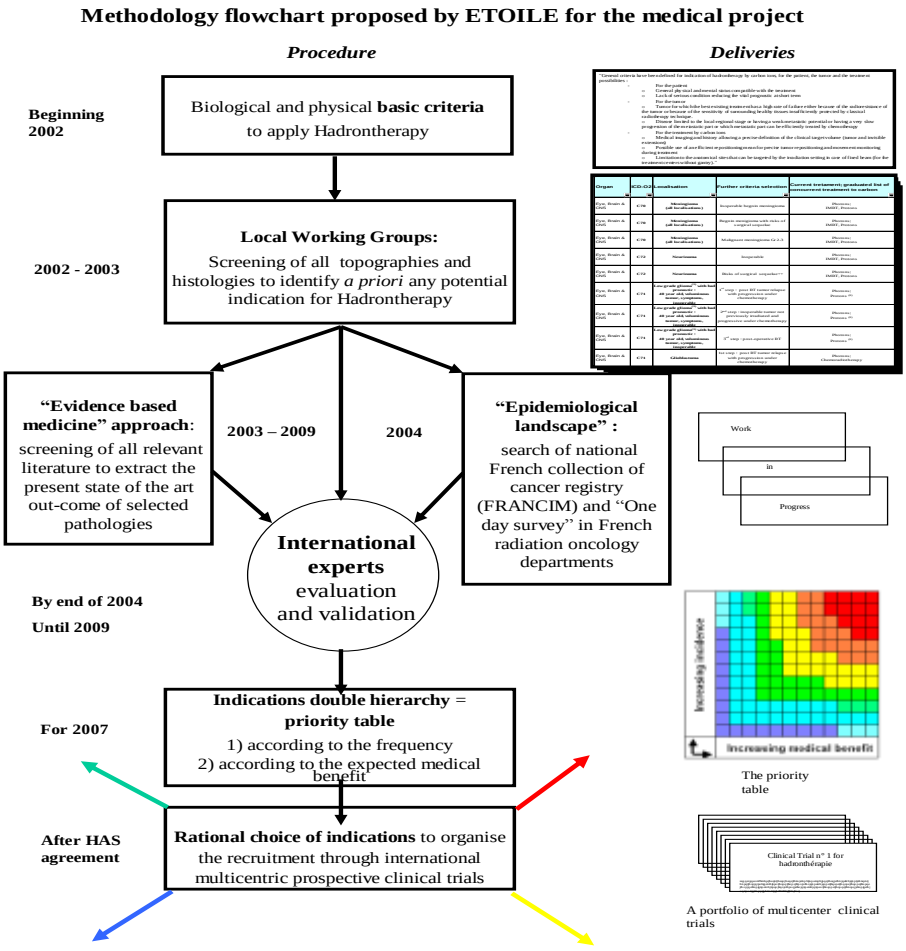


Figure 3: Method used for quantitative and qualitative study of carbon ion therapy indications

The detailed reports of assessments of the indications described in this document are available by request from the ETOILE Centre.

These assessments led to a smaller group of approximately sixty ***"confirmed" indications***. All these indications combined represent no more than around 5,000 cases per year in France. These indications were further subdivided into three groups according to the degree of benefit expected and the level of evidence:

- ***"Consolidated" indications*** (approx. 1,150 cases per year in France)
- ***"Prospective" indications*** (approx. 4,000 cases per year in France)
- ***"Exceptional" indications*** (very rare)

"Consolidated" indications (Table I) are the core indications that have been treated effectively using neutron therapy (salivary gland tumours, adenoid cystic carcinomas of the upper respiratory and digestive tracts, particularly the trachea, superficial sarcomas) and are currently treated in Japan and Germany (adenocarcinomas of the head and neck, mucosal melanomas, chordomas, sarcomas, hepatocellular carcinomas, pelvic recurrences of rectal adenocarcinomas). Their published outcomes are well above the figures obtained using non-carbon ion therapy (approximately 20–25% higher for five-year local control).

Table I: "Consolidated" indications resulting from ETOILE's work

Tumour location	*Detailed definition of indications*	*Recommended form of hadron therapy*	*Estimated incidence[§] (cases/year in France)*
Salivary gland (parotid gland) tumours	Inoperable tumours or refusal of surgery or R2 resections or local recurrences[#] All types of histology: adenoid cystic carcinomas, mucoepidermoid adenocarcinomas, acinar cell carcinomas, etc.	Carbon alone or in combination with a dose of locoregional photon therapy	≈ 100
Paranasal sinus tumours	Inoperable tumours or refusal of surgery or R2 resections or local recurrences Adenocarcinomas and adenoid cystic carcinomas	Carbon alone in primary location	≈ 250
Adenoid cystic carcinomas with skull base involvement	Inoperable tumours or refusal of surgery or R2 resections or local recurrences	Carbon alone in primary location	≈ 10
Malignant mucosal melanomas (primarily ENT)	Any location without immediately threatening metastasis Tumour without surgery if possible or emergency after R2 resections or non-irradiated local recurrence	Carbon alone in primary location; urgent treatment	≈ 40
Chordomas at the base of the skull, spine and sacrum	Any clinical presentation	Carbon or proton therapy alone in primary location	≈ 30–50
Chondrosarcomas of the axial skeletal	Base of skull	Proton therapy alone in primary location	≈ 20
	Spine and sacrum	Proton therapy or carbon alone in primary location	<10
Soft-tissue (non-retroperitoneal) sarcomas	Weak-grade M0, any histology, any location Unresectable or surgery refused or "definitive R2": R2 with no possible repeat surgery or R2 following repeat surgery or local recurrence in R2 resection	Carbon alone in primary location	≈ 100
	Non-threatening M+ with incapacitating T or rT		≈ 80
Retroperitoneal sarcomas	Following local recurrence and surgical resection: R0 or R1 and M0 (for unresectable T and R2, see above)		≈ 40
	Initial status R1 M0		
Soft-tissue sarcomas of the head, neck and limbs	"Definitive R1": R1 resection with no acceptable possibility for repeat surgery		≈ 200
Osteo- and chondrosarcomas (any location except axial skeleton)	Tumours without surgery or resections: R2, M0 M+ accepted for osteosarcomas only Discussion according to grade		≈ 10
Pelvic recurrence of rectal adenocarcinomas	Unresectable unifocal locoregional pelvic recurrences in irradiated or non-irradiated location, and M0 (CT, liver MRI, PET)	Carbon alone	≈ 200
Hepatocellular carcinomas	Single hepatocellular carcinoma, ø > 4–5 cm, unresectable, M0, not suitable for conventional treatment methods or photon therapy, no threatening comorbidity	Carbon alone in primary location	≈ 50

Notes:

[§]The annual estimated incidence is the estimated total annual number of tumours that match the detailed descriptions. This is the maximum recruitment potential. It does not take into account feasibility of treatment or the care services actually available.

[#]Local recurrence is taken to mean the reappearance of the tumour in its primary location, with no other regional or metastatic manifestation.

"Prospective" indications (Table II) are those that fall outside the categories of tumours historically treated using neutron therapy, and also characterised by substantially higher incidences than consolidated indications. Some have already been researched in prospective studies by the NIRS (high-grade gliomas, pancreatic cancers, prostate cancers, lung cancers, epidermoid head & neck cancers, etc.), sufficient time has not yet elapsed to enable us to assess therapeutic benefit. In addition, being more frequent they should be suitable for prospective randomised comparative trials once multicentre protocols can be implemented, providing material for additional assessments in the years to come. The first results published for these tumours are shown in chapter II.3, page 35.

Table II: "Prospective" indications resulting from ETOILE's work

Tumour location	*Detailed definition of indications*	*Recommended form of hadron therapy*	*Estimated incidence[§] (cases/year in France)*
Non-small cell lung cancer	Inoperable initial status, stage (UICC/AJC 1997) IA and IB: T1T2**N0** (CT, PET) M0 (brain MRI); purely endobronchial tumours excluded	Carbon alone in primary location with respiratory gating	≈ 750–1000
	Second cancer in patients who underwent radiotherapy and/or pneumonectomy >2 years ago; inoperable stage I		
	Inoperable initial status, stage (UICC/AJC 1997) IIB–IIIB limited to T3T4**N0** (CT, PET) M0 (brain MRI); purely endobronchial tumours excluded		
	Second cancer in patients who underwent radiotherapy and/or pneumonectomy >2 years ago; inoperable stage II		
Nasopharynx	Any histology Strictly local recurrences[#] after initial radiation	Protons or carbon	≈ 10
High-grade gliomas (grade 3 or glioblastomas)	Recurrence after initial radiotherapy +/- chemotherapy and progressing during chemotherapy	Carbon alone in primary location	≈ 50
	Initial treatment, possibly following surgery		≈ 300
Epidermoid ENT carcinomas	Unresectable recurrences or second location, in irradiated area and M0 (CT, liver MRI, PET) *(proposal to be assessed)* Initial status T3–T4, N ≤2, M0 of the oropharynx or oral cavity *(proposal to be assessed)*	Carbon alone	≈ 500
Prostate adenocarcinomas	Intermediate risk groups: T2b, T3a/b **and** (PSA 10–20 **and**/**or** Gleason ≥7) **and** pN0	Comparison IMRT ± hormone therapy versus carbon versus protons	≈ 1000
Highly radioresistant tumours of the digestive tract	Unresectable single nodular bile duct cancer or pancreatic adenocarcinoma, M0, not previously irradiated and not progressing during chemotherapy after 4–6 months	Carbon alone or in combination with dose of locoregional photon therapy	≈ 900
	M0 endocrine tumour of the pancreas, progressing after multiple treatments: isotopic and/or chemotherapy and somatostatin	Carbon alone in primary location	≈ 20

Notes:

[§]The annual estimated incidence is the estimated total annual number of tumours that match the detailed descriptions. This is the maximum recruitment potential. It does not take into account feasibility of treatment or the care services actually available.

[#]Local recurrence is taken to mean the reappearance of the tumour in its primary location, with no other regional or metastatic manifestation.

"Exceptional" indications (Table III) are absolutely isolated situations with no other treatment options. They include both paediatric indications that have not yet been treated using carbon ion therapy but are clearly life-threatening, and exceptionally rare, radioresistant tumours that are strictly threatening to locoregional or vital functions. These indications can certainly never be the subject of comparative studies, but nevertheless they must be discussed by experts at multidisciplinary consultation meetings and be traceable in terms of management by carbon ion therapy if this is authorised.

Table III: "Exceptional" indications proposed by ETOILE

Tumour location	*Detailed definition of indications*	*Recommended form of hadron therapy*	*Estimated incidence[§] (cases/year in France)*
Paediatric tumours	Large (more than 100 or 200 ml, depending on age), inoperable Ewing's sarcomas of the pelvis Aggressive chordomas in small children (<3–4 years) Unresectable pelvic osteosarcomas	Carbon alone in primary location	<100
Various locations, highly functional	Benign tumours or locally-invasive malignant tumours that are incapacitating and have a high risk of local recurrence (desmoid tumours, neurinomas, schwannomas, meningiomas, etc.)	Carbon alone	Very rare

The ETOILE Centre is managed according to the underlying principle of achieving financial viability by treating "consolidated" indications alone. As a result, this document will examine only these indications in terms of the comparative results of carbon ion therapy.

However, publications on other indications (prostate cancers, lung cancers, gliomas, pancreatic cancers) are growing in number. This may alter some priorities over time.

Study of "consolidated" indications to be recruited by the ETOILE Centre

Thanks to the accumulated experience of hadron therapy (using carbon, neon or helium) and the most recent work of the NIRS and GSI, experts have been able to provide an estimate of the benefit achieved by carbon ion therapy in terms of an **approximately 20–25% absolute increase in local control**, depending on the case in question. This is a very significant gain for oncology. The estimate is based on a range of arguments and is not based on consultation of prospective comparative clinical data alone.

These indications are in fact a series of "niche" diseases that sometime have very low incidences but represent genuinely difficult-to-treat tumours.

There are no recently published randomised trials comparing hadrontherapy and conventional treatments, but such studies are currently ongoing in Europe (see chapter II.4, page 38). Series that have been published, including those on conventional treatments, are often very small.

In many cases we have referred to retrospective series of conventional treatments whose results are often substantially overestimated[8] if compared to the intent-to-treat approach taken in almost all carbon ion therapy series. The differences shown here are therefore probably underestimates.

"Traditional" publications are generally made either to illustrate a treatment procedure by combining all histological types for a given anatomical region, or to evaluate the results of treatments for a specific disease defined by its histopathology, with tumours in various locations. Because the tradition in medical scientific publishing is to exclude tables of individual analytical data of reported cases from published papers, it is very often impossible to determine which characteristics correspond to which category, as all categories are combined in published data.

In addition, for some rare tumours that behave in approximately similar ways, there are sometimes no data whatsoever on some sub-locations that are even rarer. The authors propose to extrapolate from overall data to these sub-locations that have been little explored but are of the same histopathological nature.

This document brings together as much data as possible and includes tables that summarise all the interpretable data from the literature, updated in early 2012 for conventional treatments and in early 2013 for carbon ion therapy. An electronic CD/DVD database or USB key containing all the hundreds of articles studied and cited is available on request from GCS-ETOILE. The February 2010 preliminary report of HAS, France's High Health Authority, on carbon ion therapy concludes as follows:

> *"Analysis of the literature was based on 14 publications on a heterogeneous group of 11 indications, for a total of 22 retrospective and prospective studies.*
> *Analysis was restricted by the limited amount of data available and low methodological quality (non-comparative studies, phase I and II studies, small case numbers, mixed populations and locations). In addition, there are no studies providing comparison with other treatments, in particular high-tech radiotherapy (proton therapy, stereotactic radiotherapy). The reader is warned that the data do not always provide comparisons.*
>
> *With these caveats, the data suggest the following:*
> – *Carbon ion therapy appears to be potentially higher-performing than conventional radiotherapy in the following indications: adenoid cystic carcinomas of the head and neck, salivary gland tumours without full resection, chordomas and chrondrosarcomas at the base of the skull, non-small cell lung tumours.*
> – *Carbon ion therapy seems to be potentially equivalent to other very high-tech types of radiotherapy for the following indications: chordomas and chrondrosarcomas at the base of the skull, indications of the head and neck, all locations combined (descriptive systematic review by Lodge et al (25)), non-small cell lung tumours (systematic review by Grütters et al (38)), sarcomas of the soft-tissues and axial skeleton (studies by Kamada et al. (95)).*

[8] This overestimate of the outcomes of conventional treatment versus carbon ion therapy is the result both of retrospective procedures and of the fact that tumours treated with photon and proton therapy are often smaller than those treated with carbon ion therapy. The latter often include advanced forms and even postsurgical tumour recurrences, particularly at the NIRS in Japan.

- *The potential of carbon ion therapy appears to be undefined for the following indications: unresectable local recurrences of rectal tumours, large hepatocellular carcinomas, prostate tumours, cervical tumours.*
- *Carbon ion therapy can cause late toxicity. This has been associated with the following indications in particular: chordomas and chrondrosarcomas at the base of the skull, sarcomas of the soft-tissues and axial skeleton, choroidal melanomas, ocular tumours.*

Overall, both analysis of the most recent literature published to date and the reports by evaluation agencies indicate that there is insufficient information available, particularly from comparative studies, to conclude definitively on the efficacy/safety balance of carbon ion therapy. It appears to be a promising technique for the treatment of some inoperable, unresectable or radioresistant tumours surrounded by radiosensitive healthy tissue and is currently undergoing clinical research.

In particular, additional studies are needed to define the following:

- *Technical parameters: dose distribution, relative biological efficacy according to the tissues passed through, ballistic calculation*
- *Indications*
- *Methods of administration: dose fractionation, isolated or combined administration*
- *Medium- and long-term morbidity and mortality data*
- *Characteristics of the populations treated*
- *Characteristics of the tumours treated*
- *Data collation on toxicity and the risk of radiation-induced cancer*
- *The place of carbon ion therapy in relation to other treatment options, particularly proton therapy*

Research currently in progress in France and abroad should provide these data, particularly in terms of patient recruitment, definition of target populations, protocols and long-term follow-up, in conjunction with the main players in the health care system, including the INCa [National Cancer Institute].

Scientific vigilance must be ensured in order to monitor the development of this technology and collation of additional data."

Since this HAS report was written, five new hadron therapy facilities have become operational worldwide (Heidelberg, Gunma, Chiba II, CNAO, Tosu-Saga), and construction of two more has begun (MedAustron in Austria, Kanagawa in Japan). The number of patients treated has increased by approximately 3,500 to more than 10,000 to date. The longest follow-up period, that of the Japanese cohort, is 19 years, while the median follow-up period is around 7 years. Approximately 100 additional publications[9] are available, and phase II and III clinical trials have begun in Europe. These conclusions should therefore be reviewed before a new assessment by the HAS is issued.

However, although more data are now available and have been processed meticulously, the concept of randomised phase III trials, as conducted for drugs, continues to be imposed, in contradiction to the approach described above. In the absence of experts accustomed to methodological issues concerning physical cancer treatments, specific, in-depth examination of whether this approach is relevant to hadrontherapy is difficult to obtain. Carbon ion therapy is in fact merely one step in the long history of the progress of radiotherapy: a constant increase in the difference between the dose administered to the target and the dose to healthy tissue. The methodological discussions must therefore be included in this essential issue, and not only as explanations of the work performed. This issue is addressed in the following chapter.

I.2. Discussion about the Place and the Form of Comparative Clinical Trials in Radiotherapy and In Hadrontherapy

Specificity of evaluation of technological innovation, particularly in radiotherapy

The issue of whether phase III randomised trials, as used in drug research, is relevant to this type of therapy has been raised repeatedly by experts in recent years (Bentzen; Suit). A summary of this issue is

[9] 331 referenced publications in MedLine since 1968; approximately 175 in the 10 years from 1999 to 2009 and 100 from 2010 to the present. In other words, the rate of publication has doubled in the last 2 years.

provided in French radiotherapists' collective assessment in the *Radiotherapy White Paper: SFRO 2013* (White Paper; chapter 8.2.2, pages 109–110). This document recalls that almost all technical progress in radiotherapy has been based on the pursuit of a single physical, measurable aim, namely minimising the dose to healthy tissues and maximising the dose to tumour tissue, in a context of ever more rigorous quality assurance. The underlying biological principle, which is verified in absolutely all cases and is not contested by anyone, is the relationship between dosage and effect. In addition, new technologies do not involve new therapeutic principles. All types of radiation and all types of equipment act in the same way; the only thing that changes is their level of performance and quality in terms of operational variables that give rise to directly measurable parameters that can be evaluated immediately in quantitative terms (dose distribution at a level of accuracy of a few percentage points, millimetre accuracy of repositioning, etc.). Many specific, highly sophisticated tools have been developed for this purpose (dose/volume histogram, gamma index comparison, 3D image coregistration, imaging guided therapy, tracking and respiratory gating, etc.). Actually, dose is effective only where it is delivered and always acts in the same way within certain quantitative limits, so a new type of radiation cannot cause new, unexpected or unknown side effects as a new molecule may do. For carbon ions, the dose searching studies in USA, Japan and Germany have already provided data on the tolerance levels of organs at risk. Further refinements may be necessary, especially with changes in dose fractionation, but these can be accommodated within the ongoing studies in Europe. This means there is no need to evaluate hypothetical delayed side effects that might outweigh therapeutic benefits, as often seen in pharmacology. This means, that in general, the issue of risk/benefit ratio does not arise in radiotherapy provided good practice regulations are complied with, particularly maximum doses to organs-at-risk. These limits were established by international consensus. In addition, technical issues have been continually developing for several decades, each one building on the one that preceded it. They result from major investments in resources and staff which cannot be made to conduct a single trial: these investments represent the use of a working tool that is constantly being renewed and maintained.

However, the main aim to which "priority is given by institutional players through phase III trials is to demonstrate a benefit in terms of survival time, other aims being secondary" (White Paper). These other aims include quality of life, good treatment tolerance and cost-effectiveness. This aim, survival time, is affected by many other variables that act as confounding factors minimising or masking the benefit of radiotherapy, which by its nature is local. In addition, these phase III trials require large numbers of patients recruited for periods of several years, with a long follow-up times, to see the local impact of treatment – all the more so because of these confounding factors. **For example, the impact of radiotherapy on survival time in breast cancer appears at more than ten years, but radiotherapy is a vital part of breast-preserving treatment. No technical progress in this treatment could be tested in phase III trials using survival time as a criterion.** Therefore, evaluation of a procedure would result in its being approved only after it had been replaced by others and become obsolete as a result of continuing technological development. This problem also arises for new drugs, which appear faster than would be possible if they were approved on the basis of survival time alone. Investigators therefore define surrogate outcomes such as early response on functional scintigraphy (PET, etc.). In radiotherapy, these surrogate outcomes can be precise, reproducible physical measures: calculation and modelling of dose distribution.

The issue of phase III trials also raises ethical and regulatory problems concerning radiation protection precautions (White Paper), which are very restrictive in France. In fact, by law radiotherapists must use the best available means to minimise the dose to healthy tissue as far as possible. Once direct, reliable measurements of this dose exist, it is no longer possible to test the result on indirect long-term criteria by asking half the patients participating in the research to receive a higher dose than technically possible. The attempts that have been made to conduct such research have often been abandoned due to insufficient numbers of volunteer patients (White Paper).

These considerations lead the SFRO (White Paper) to conclude that "phase III randomised trials cannot be the only method of evaluating therapeutic progress in oncology, particularly radiotherapy. Other methods must be developed and promoted." These methods must be suited to the goals pursued. They may be randomised or non-randomised phase II trials, cohort studies, very long-term observational

follow-up studies (10–20 years for analysis of treatment de-escalation in Hodgkin's disease, impact on the risk of secondary cancer for intensity-modulated radiotherapy, etc.), *in silico* studies (the aim of the ROCOCO international platform based in Maastricht), modelling of health economics, etc.

The Purpose of Evaluating a Technical Innovation in Radiotherapy

When evaluating an innovation in radiotherapy, the main aims must be as follows:

- Reproducibility of the method used and quality of routine use of the method in terms of dosing
- If needed, dose escalation studies with short-, medium- and long-term efficacy and toxicity criteria have to be conducted
- Users' know-how, particularly adjusting their knowledge to new treatment methods. It may actually be necessary to adjust methods for prescription and definition of target volumes. Adjustments may result from patient cohort follow-up. Two examples are as follows: new dose calculation algorithms are more accurate than previous versions but by virtue of this they correct the routine dosing underestimates that have characterised physicians' prescription procedures. Failure to adjust for this might, paradoxically, result in routine underdosing and more treatment failures, particularly in thoracic tumours. This is a highly complex technical issue. Similarly, more accurate, better targeted dose distribution in advanced radiotherapy procedures such as IMRT and VMAT makes less allowance for inaccurate definition of target volumes. Recurrences that have remained unknown for years might reappear and make it necessary to reconsider practices, as with the base of the skull in head & neck radiotherapy. There too, only critical follow-up of patient cohorts can bring this to light. In a randomised trial, an effect such as this would lead us to conclude that the new technique was inferior when in fact the problem was one of learning and adaptation to progress.
- The cost of technical progress. This is a crucial point, as all progress pursues a single aim. It is important to know what degree of progress justifies what level of investment by all those involved. For treatments that require particularly large investments, such as hadrontherapy, health economics must be given priority in trials to be conducted.
  It may therefore genuinely be necessary to measure medical progress in order to to compare with the additionnal cost. This is the principle behind establishing a causal relationship in phase III trials. With the caveats made above, this may justify the conduct of phase III trials, but only for common diseases with a major impact on the cost of health care. For example, it seems inevitable that a randomised trial will soon be conducted into prostate cancer, comparing proton therapy and IMRT/VMAT, then carbon ion therapy, as the incidence of prostate cancer means the costs involved are potentially huge. It remains to be seen whether patients would agree to such a trial; in France they probably would, as there is little access to proton therapy, but in the USA it is unlikely.

Discussion of the position of the ETOILE project and carbon therapy in this context

Carbon ion therapy is based on the same principle as radiotherapy in general. It differs from other types of radiotherapy only quantitatively: high accurate targeting, limited dose in depth, low diffusion of particles outside their intended route and very high ionisation density at destination; these factors give it its ability to treat highly radioresistant tumours that do not respond to other procedures.

Because of these characteristics and its high cost, the procedure was initially reserved for diseases considered extreme as a result of their rarity and radioresistance. This means it is a technical improvement on neutron therapy and proton therapy, and was therefore initially used on tumours with poor outcomes following other X-ray or even proton therapies.
In this particular context, the medical potential of carbon ion therapy is therefore not open to dispute or doubt.

The "modern"approval of carbon ion therapy (its development phase in Japan from 1994 and in Europe from 1998) was therefore, very logically, based on phase I/II dose-escalation studies followed by phase II trials more extended than it is traditionally the case in Europe. In fact, during these phase II trials

(described as "late" *vs* early), the Japanese chose to evaluate safety and the dose/effect ratio, and also went to the lengths of evaluating the treatment efficacy hypothesis. Finally, to boost the statistical power of their results the trials included more patients than usual for phase II (50 to 100 patients or even more, compared to the usual figure of 15 to 30). However, in practice and by Western custom efficacy and reliability are usually evaluated in phase III. One might therefore wonder whether it is worth continuing phase III clinical trials when for certain diseases the in-depth phase II trials conducted in Japan have provided answers to all the expected questions relating to medical and scientific research, making it possible to incorporate this therapy into current medical practice in all safety. In view of this, for the indications in which the most research has been conducted in both Japan and Europe, proposing to new series of patients, having no real therapeutic option, that they take part in phase III research that might be described as redundant, becomes very debatable ethically. Phase III trials do provide a little more accuracy on matters of efficacy, but in this context, for these rare diseases that have already been rigorously evaluated and are currently treated in Japan, this makes no sense.

The results of this initial phase of evaluation are very clear: carbon ion therapy provides results that have never before been achieved in very advanced tumours. These results are reproducible at different treatment facilities, require only a few sessions and have low toxicity. Although conditions are *prima facie* unfavourable to carbon ion therapy (because it is compared with trials of other treatment that are retrospective, include less advanced cases and involve small cohorts – all conditions known to lead to an overestimate of outcomes), the differences in outcomes are nevertheless very substantial: between 20% and 25% or more in terms of local control and even survival.

The current situation therefore raises a new issue that has not yet been mentioned here: **the ethical appropriateness of randomised trials for rare, slow-progressing tumours when the difference between treatment outcomes seems so great.** This principle has also been hotly debated for many years, particularly for placebo-controlled trials, and led to the notion of a balanced clinical position and the concept of *equipoise*, a term coined by B Freedman. This ethical concept developed and is included in the 2008 version of the Declaration of Helsinki, but it is perhaps the collective version of equipoise, proposed by N Johnson et al, that applies to radiotherapy and hadrontherapy. Referring to these proposals, which are difficult to contest, when more than 70% of experts believe that there is a real difference in outcomes, it becomes unethical to conduct randomised trials.

For the first indications of carbon ion therapy, those described as "consolidated indications" in this document, the experts do not doubt that carbon ions are superior to non-carbon treatments (except for chrondrosarcomas at the base of the skull and medium-sized hepatocellular carcinomas, for which proton therapy outcomes are equally good; however, this is known and has been taken into account in Table I on page 8 and analysed in Tables XIII and XIX).

To summarise, it is clear that consolidated indications do not require randomised trials in order to be considered validated indications of carbon ion therapy. Obviously, this does not mean that this will necessarily be the case for prospective indications (see below).

The ETOILE project rests on this very cautious principal: if all of France is included (approximately 1,200 cases per year), and all the more so if overseas cases are included, **consolidated indications are sufficient to ensure recruitment levels necessary for the ETOILE Centre to be financially viable**. They can therefore provide a basis for the introduction of this technology in France. While waiting for this, and because a prospective study is also an opportunity for patients to receive an innovative treatment, a public funded clinical research programme has been started in conjunction with the CNAMTS (the French National Health Insurance Fund). Building on that beginning, development will then concern prospective indications, using a more traditional approach, including randomised trials, especially as very promising results are being announced (for pancreatic adenocarcinoma, uterine sarcomas, lung cancers, etc.).

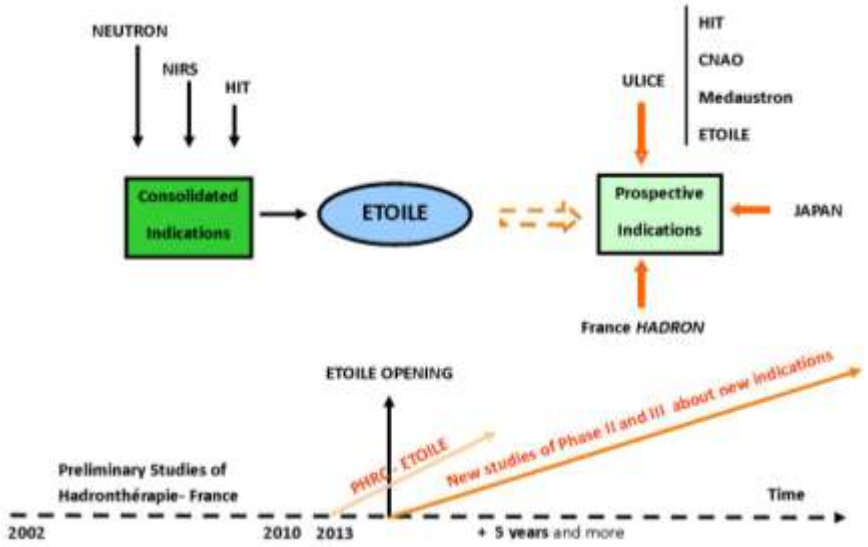
Conclusion for clinical research and a suitable evaluation to ETOILE and hadrontherapy

The ETOILE project has identified two groups of indications:

1) Consolidated indications, which can immediately serve as the basis for initial carbon ion therapy in France. The procedure followed by GCS-ETOILE to validate these indications is described in the preceding chapter, and is very similar to the procedure used by the HAS for its ongoing evaluation of IMRT in cancers of the anal canal and cervix:[10]

   [page 17] The method proposed is based on the following:
   - *Critical analysis of the scientific data identified (making it possible to provide information on the evaluation criteria established in chapter 4)*
   - *The point of view of a multidisciplinary group of health care professionals, with explanations provided, and the points of view of patient representatives, who will be brought together in a working group*
   - *Consultation of a reading group*

2) Prospective indications, which will subsequently be explored further in prospective clinical studies (if needed, randomised trials) in conjunction with European facilities (the ULICE group) and possibly Japanese facilities (NIRS, Gunma, Saga, Hyogo).
3) With the opening of the ETOILE Centre, GCS-ETOILE thanks to European collaboration will then make some types of carbon ion therapy available to French patients, particularly as a result of a prospective randomised trial conducted in collaboration with the Heidelberg facility and possibly that of CNAO in Pavia. Funding has been provided by the 2011 public funded clinical research programme and the CNAMTS. The trial sponsor is Hospices Civils de Lyon (*Lyon University Hospitals*), partner of GCS-ETOILE. Patient recruitment is due to begin in late 2013, with the trial title *"Evaluation médicale et économique prospective randomisée de la radiothérapie par ions carbone (carbonethérapie) pour les sarcomes et carcinomes adénoïdes kystiques inopérables ou en résection R2" ("Prospective, randomised medical evaluation and health economics of carbon ion radiotherapy for inoperable or R2 resected sarcomas and adenoid cystic carcinomas").*
4) Finally, the ETOILE Centre has the commitment to provide sufficient resources for multidisciplinary consultation and clinical research for the evaluation and long-term follow-up for all patients treated. In fact, the set-up of the ETOILE Centre (a unique national facility with specific equipment for carbon ion therapy) will make it the ideal tool for comparative assessment of the best outcomes of conventional radiotherapy (including proton therapy) and carbon ion therapy.



[10] Link to information on the HAS website (in French): http://www.has-sante.fr/portail/jcms/c_1364144/fr/evaluation-de-la-radiotherapie-conformationnelle-avec-modulation-dintensite-dans-les-cancers-du-col-uterin-et-du-canal-anal-note-de-cadrage

Figure 4: Timeframe for incorporation of various indications into ETOILE's work

References:

***Bentzen SM**. Randomized controlled trials in health technology assessment: overkill or overdue? Radiother Oncol. 2008 Feb;86(2):142–7.*

***Suit H**, Kooy H, Trofimov A, Farr J, Munzenrider J, DeLaney T, Loeffler J, Clasie B, Safai S, Paganetti H. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. Radiother Oncol. 2008 Feb;86(2):148–53.*

***Radiotherapy White Paper:** SFRO 2013*
[http://www.sfro.org/sfro_pro/media/pdf/Livre_blanc_SFRO_2013.pdf]

***Freedman, B**. (1987) 'Equipoise and the ethics of clinical research'. The New England Journal of Medicine, 317, (3):141–145.*

***Johnson N**, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? J Med Ethics. 1991 Mar;17(1):30–4.*

***Karlawish JH**, Lantos J. Community equipoise and the architecture of clinical research. Camb Q Health Ethics. 1997 Fall;6(4):385–96.*

II. Updated Medical Data on Carbon Ion Therapy

II.1. Update on Clinical Experience (USA, Japan, Europe)

The acquired clinical experiences are different on the three continents

In the USA patients received hadron therapy from 1957 using helium ions (^{4}He) in California, at the Lawrence Berkeley National Laboratory, then from 1975 to 1993 using various heavier ions – carbon (^{12}C), neon (^{20}Ne), silicon (^{28}Si) and argon (^{40}Ar) – at the BEVALAC. Only a few patients have received carbon ion therapy: most have been treated with neon, which is twice as heavy.

Table IV: Treatments administered between 1954 and 1993 at the LBNL, USA

Lawrence Berkeley National Laboratory (USA)		
Protons	***1954–1957***	***30 patients***
Helium	***1957–1987***	***2,054 patients***
Ions (neon n = 299, carbon, silicon, argon)	***1975–1993***	***433 patients***
Total	***39 years***	***2,517 patients***

This experience was technologically and medically essential in **demonstrating the feasibility** of treatments. It no longer has a great deal of medical value, but it remains essential for **evaluating long-term toxicity**, particularly the risk of secondary cancers. In fact, the risk of secondary cancer is thought to depend on particle mass, so neon ions should be more toxic than carbon ions. As more than 20 years have passed since these treatments were used, this discussion can be clarified and, no doubt, closed, at least in epidemiological terms. Data on the carcinogenicity of ions from the USA are presented later in this paper.

Japan: Since 1994 a contemporary experience of carbon ion therapy has been gained in Japan were more than **8,000 patients have been treated**. Five conclusions can be drawn from this experience, which is still growing rapidly:

- Carbon ion therapy has the potential to expand to **national scale**, with as much as five dedicated facilities all over Japan in five years' time.
- Construction of these facilities may become **industrial**, with three or four competing industrial groups.

- A very large **number of indications** (Figure 5) can be explored, thanks to **passive beam delivery**, which is a little less beneficial in terms of dosing but less expensive and much more flexible, and can be used for all tumours, including mobile tumours (of the liver, lung or pancreas).
- The use of **hypofractionation** (i.e. treating patients in a small number of sessions, typically between 1 and 16), which entails a substantial financial advantage.
- Study and description of many **protocols that act as points of reference** and an operational basis for all facilities worldwide.

Unfortunately, this experience is insufficient for Western health authorities, as it includes no randomised comparative trials. Although there are very convincing comparisons for several indications, with spectacular results, these are historical comparisons or comparisons involving different cohorts. This experience is summarised in the updated comparative tables below.

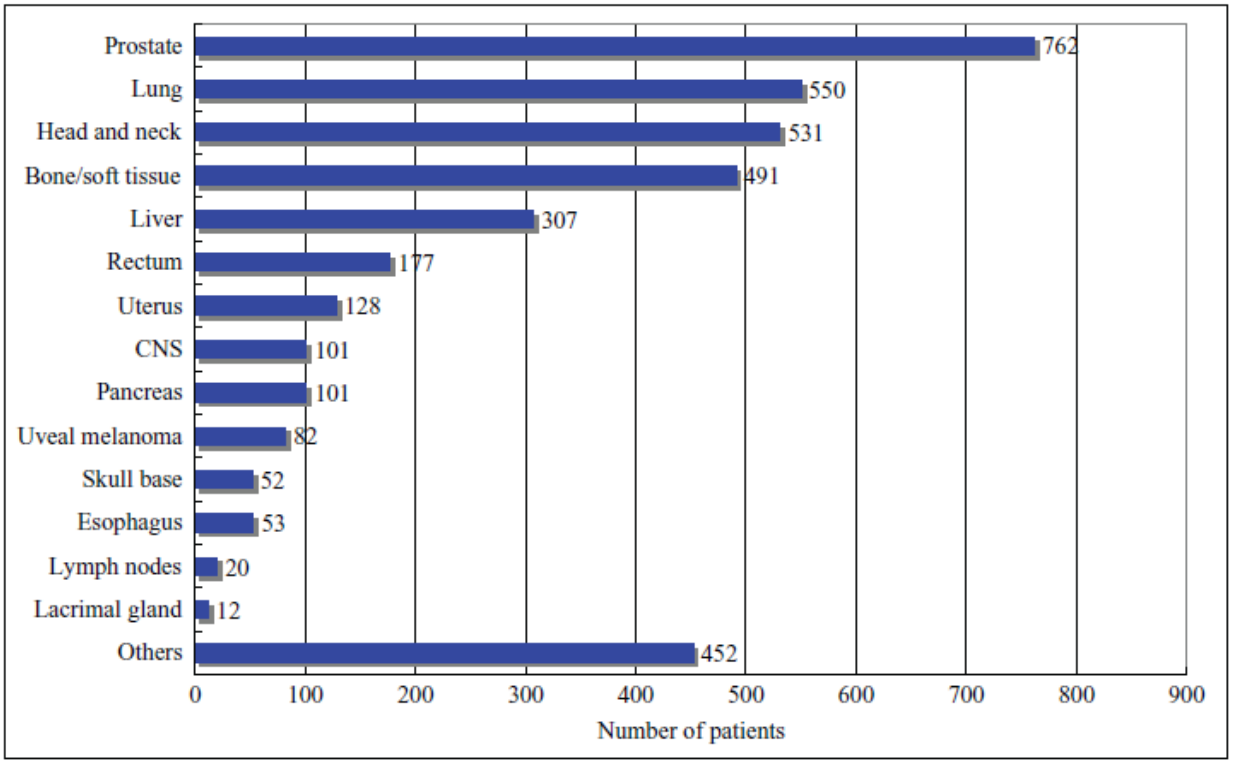


Figure 5: Numbers of tumours treated using carbon ion therapy at the NIRS (Chiba, Japan) [2008 New J. Phys. 10 075009]

In Europe, where projects involving heavy ions have been discussed since the 1980s (EULIMA, Nice 1998), the first concrete development occurred in Germany in 1998, when the first patients received carbon ion therapy in Darmstadt (GSI nuclear research facility) between 1998 and February 2008, and then in Heidelberg (HIT, University Hospital Heidelberg) starting November 2009. Approximately 450 patients have been treated at Darmstadt, and approximately 1200 at Heidelberg since the opening of HIT. Thus the experience gained in Germany to date includes **approximately 1,650 patients treated** by the same medical team (University Hospital Heidelberg under Prof J Debus) following the same principles: a horizontal beam with active delivery.

Treatment conditions in Europe to date are therefore more limited than those in Japan (which include horizontal, vertical and oblique beams and passive delivery with respiratory gating). As a result, experience in Europe includes only **head and neck tumours**. These limits will rapidly disappear, as Italy opened its CNAO facility in Pavia in September 2011 and since November 2012 has been administering carbon ion therapy with active delivery but horizontal and vertical beams; and HIT even launched the world's first isocentric rotating carbon ion beam in October 2012. This will allow all parts of the body to be irradiated. Most experience in Europe, then, has been gained in Germany. It has yielded the following findings:

- The experience gained in Japan and the USA is **reproducible**. The outcomes obtained in Germany are comparable to those obtained in Japan.
- Carbon ion therapy is a powerful **coordinator of scientific and technological collaboration**, with the European research consortiums ENLIGHT, ULICE, PARTNER, ENVISION and INTERVISION. These coordinate and boost hadron therapy in Europe with the support of FP7 (the 7th European Framework Programme for Research and Technological Development).
- **The development of hadrontherapy in Europe** must not be the responsibility of a single industrial. Instead, it requires synergy between research bodies, public hospitals and health insurance providers on the one hand, and voluntary coordination on a fairly large scale, at least national, on the other.
- Finally, **phase III randomised comparative clinical trials** are possible, particularly if they involve international cooperation within Europe.

II.2. Updated Comparative Clinical Data for Consolidated Indications[11]

(Information highlighted in yellow post-dates the document submitted to the HAS in September 2009.)
(Information highlighted in pale blue comprises the June 2013 update.)

Table V: List of the relevant clinical entities:

Tumour location	Detailed definition of indications	Recommended form of hadron therapy	Incidence in France
Salivary gland (parotid gland) tumours	Inoperable tumours or refusal of surgery or R2 resections or local recurrences[#] All types of histology: adenoid cystic carcinomas, mucoepidermoid adenocarcinomas, acinar cell carcinomas, etc.	Carbon alone or in combination with a dose of locoregional photon therapy	≈ 100
Paranasal sinus tumours	Inoperable tumours or refusal of surgery or R2 resections or local recurrences Adenocarcinomas and adenoid cystic carcinomas	Carbon alone in primary location	≈ 250
Adenoid cystic carcinomas with skull base involvement	Inoperable tumours or refusal of surgery or R2 resections or local recurrences	Carbon alone in primary location	≈ 10
Malignant mucosal melanomas (primarily ENT)	Any location without immediately threatening metastasis Tumour without surgery if possible or emergency after R2 resections or non-irradiated local recurrence	Carbon alone in primary location; urgent treatment	≈ 40
Chordomas at the base of the skull, spine and sacrum	Any clinical presentation	Carbon or proton therapy alone in primary location	≈ 30–50
Chondrosarcomas of the axial skeleton	Base of skull	Proton therapy alone in primary location	≈ 20
	Spine and sacrum	Proton therapy or carbon alone in primary location	<10
Soft-tissue (non-retroperitoneal) sarcomas	Weak-grade M0, any histology, any location Unresectable or surgery refused or "definitive R2": R2 with no possible repeat surgery or R2 following repeat surgery or local recurrence in R2 resection	Carbon alone in primary location	≈ 100
	Non-threatening M+ with incapacitating T or rT		≈ 80
Retroperitoneal sarcomas	Following local recurrence and surgical resection: R0 or R1 and M0 (for unresectable T and R2, see above)		≈ 40
	Initial status R1 M0		
Soft-tissue sarcomas of the head, neck and limbs	"Definitive R1": R1 resection with no acceptable possibility for repeat surgery		≈ 200

[11] Please see the detailed explanations in the preamble for the detailed definition of consolidated indications.

Osteo- and chondrosarcomas (any location except axial skeleton)	Tumours without surgery or resections: R2, M0 M+ accepted for osteosarcomas only Discussion according to grade		≈ 10
Pelvic recurrence of rectal adenocarcinomas	Unresectable unifocal locoregional pelvic recurrences in irradiated or non-irradiated location, and M0 (CT, liver MRI, PET)	Carbon alone	≈ 200
Hepatocellular carcinomas	Single hepatocellular carcinoma, ø > 4–5 cm, unresectable, M0, not suitable for conventional treatment methods or photon therapy, no threatening comorbidity	Carbon alone in primary location	≈ 50

Adenoid cystic carcinomas (ACCs):

Although these tumours are rare, three trials in patients with adenoid cystic carcinomas have been published. In particular, these included ACCs of the salivary glands and paranasal sinuses.

1) A German phase I/II trial conducted by Shultz-Ertner in 2003 evaluated the feasibility and toxicity of combination therapy with photons and carbon ions in the treatment of locally-advanced adenoid cystic carcinomas. A total of 16 patients were recruited, with tumours located in the nasopharynx (3 patients), ocular orbit (3 patients), cheek (3 patients), ethmoid bone (2 patients), maxillary sinuses (2 patients), parotid gland (2 patients) and tongue (1 patient). One half of the patients (8 patients) were being treated for a recurrence, and the other half for a primary tumour (8 patients). All had histologically-confirmed ACC with macroscopic involvement of the base of the skull on scans or MRI. Treatment consisted of initial proton irradiation at a dose of 54 Gy, followed by a carbon ion boost of 18 GyE (3 × 6 GyE). Photon irradiation was delivered at 1.8 Gy, fractionated, five times per week, as conformal, stereotactic or intensity-modulated therapy. The maximum dose to the optic nerves, chiasma and brainstem was kept below 54 Gy. No treatment interruptions were observed. Three locoregional relapses were observed; the median follow-up time was 12 months (3–43 months). The 1-year and 3-year locoregional control rates were 80.0% and 64.6% respectively. The overall 1-year and 3-year survival rates were 100% and 83.3% respectively. Two patients presented grade 3 acute toxicity. No cases of late toxicity of grade 3 or above were observed. These results were updated in 2004, with 21 patients recruited. The 3-year locoregional control rate and the 3-year overall survival rate were 62% and 75% respectively.

2) The second study by the same team was a retrospective analysis of a series of 29 patients (including the 16 from the previous study), all treated according to the same regimen of photons (total dose 54 Gy) with a carbon ion boost (18 GyE). The median follow-up time was 16 months (2–60 months). The 2-year and 4-year overall survival rates were 86.6% and 75.8% respectively. The relapse-free survival rate at two and four years was 71.5% and 53% respectively. The 2-year and 4-year local control rates were 77.5%. Two patients presented grade 3 acute mucitis. No cases of grade 3 or 4 late toxicity were reported.

3) The third trial was a phase II trial conducted by Mizoe et al and updated by Hasegawa et al at Japan's NIRS. 151 patients were recruited between April 1997 and February 2011, all with ACC. They all had a histologically-confirmed, measurable ENT tumour. Treatment consisted of carbon ion irradiation alone, either at a dose of 64 GyE in 16 fractions over 4 weeks, or at a dose of 52.8 GyE in 18 fractions over 6 weeks. The 5-year local control rate was 74%; the 5-year overall survival rate was 72%.

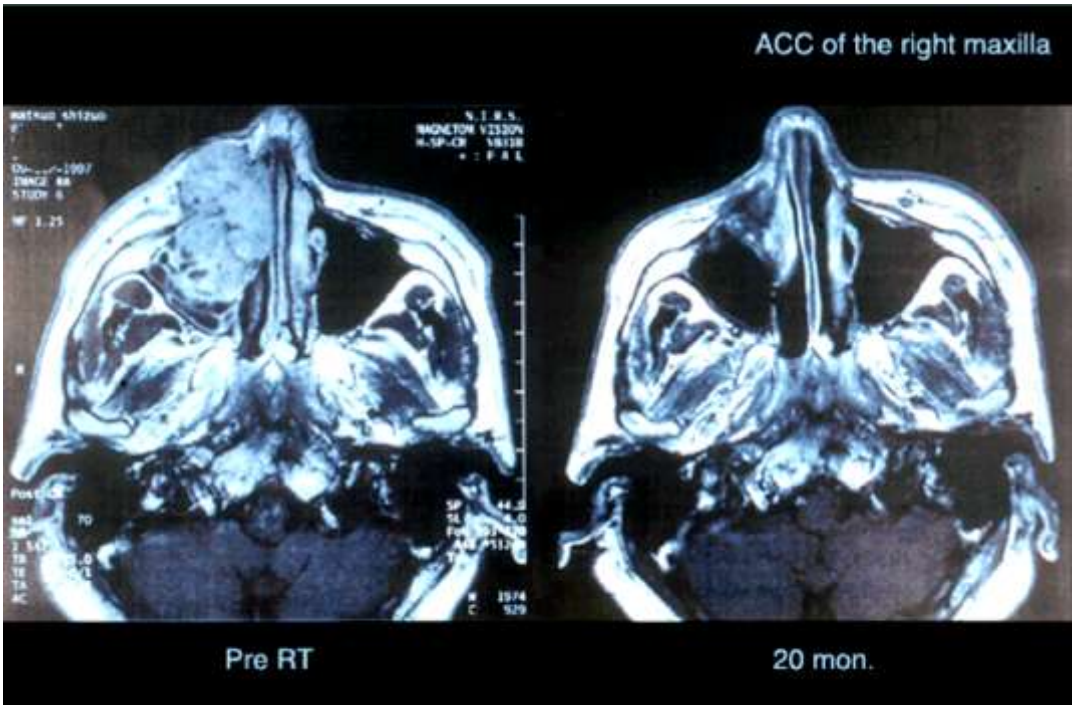


Figure 6: Example of an adenoid cystic carcinoma treated at the NIRS (Chiba, Japan); outcomes shown in Table VI

Table VI

Indication: Adenoid cystic carcinoma				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Douglas 2000	Neutrons (159)	Retrospective	N/A	5-yr OS: 72%
Prott 2000	Neutrons (72)	Retrospective	N/A	5-yr OS: 53%
Brackrock 2005	Neutrons (71)	Retrospective	5-yr LC: 63%	5-yr OS: 65%
Bittner 2008	Neutrons (20, all trachea)	Retrospective	5-yr LRC: 54.1% 5-yr DFS: 28.4%	5-yr OS: 89.4%
Pommier 2006	Protons (23)	Retrospective	N/A	5-yr OS: 77%
Hasegawa 2011	**Carbon ions (151*)**	**Prospective phase I/II**	**5-yr LC: 74%**	**5-yr OS: 72%**
Schulz-Ertner 2004	**Carbon ions + photons (21)**	**Prospective phase I/II**	**3-yr LRC: 62% 3-yr DFS: 40%**	**3-yr OS: 75%**
Weighted mean difference in 5-year local control rates between carbon ions (71.5%) and neutrons (61%) = +10.5%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
*Including 78 T4 and 40 post-surgical recurrences

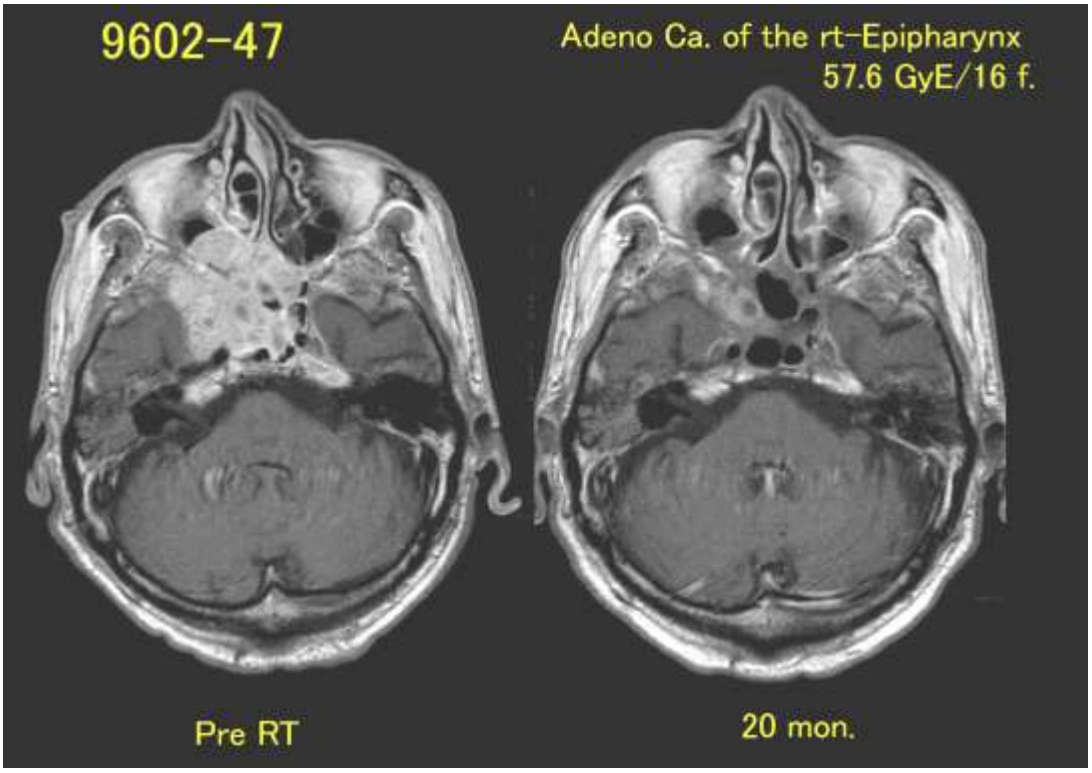


Figure 7: Example of an adenocarcinoma of the paranasal sinuses, here the sphenoid sinus, treated at the NIRS (Chiba, Japan); outcomes shown in Table VII

Table VII

Indication: Nasal cavity and paranasal sinus cancer				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Duthoy 2005	Photon IMRT (39)	Retrospective	4-yr LC: 68% 4-yr DFS: 59%	4-yr OS: 59%
Daly 2007	Photon IMRT (36)	Retrospective	5-yr LC: 58% 5-yr DFS: 55%	N/A
Dirix 2007	Photon IMRT (25)	Retrospective	2-yr LC: 81% 2-yr DFS: 77%	5-yr OS: 65%
Madini 2009	Photon IMRT (84)	Retrospective	5-yr LC: 70.7%	5-yr OS: 58.5%
Truong 2009	Protons (20)	Retrospective	2-yr LC: 86% 2-yr LRC: 86% 2-yr DFS: 31%	2-yr OS: 53%
Zenda 2011	Protons (39)	Retrospective	1-yr LC: 77.0% ***3-yr PFS: 49.1%***	***3-yr OS: 59.3%***
Fukumitsu 2011	Protons (17)	Retrospective	2-yr LC: 35% ***5-yr LC: 17.5%***	2-yr OS: 47.1% ***5-yr OS: 15.7%***
Mizoe 2007	**Carbon ions (117)**	**Prospective phase II**	**5-yr LC: 63.3–75.7%***	**5-yr OS: 25.8–44.6%†**
Weighted mean difference in 5-year local control rates between carbon ions (69.2%) and protons (36%) = +33.2%; between carbon ions and photon IMRT (61.8%) = +7.4%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
*For nasal cavities and paranasal sinuses respectively.
†The markedly low value of OS when compared to LC is due to the development of visceral metastases.

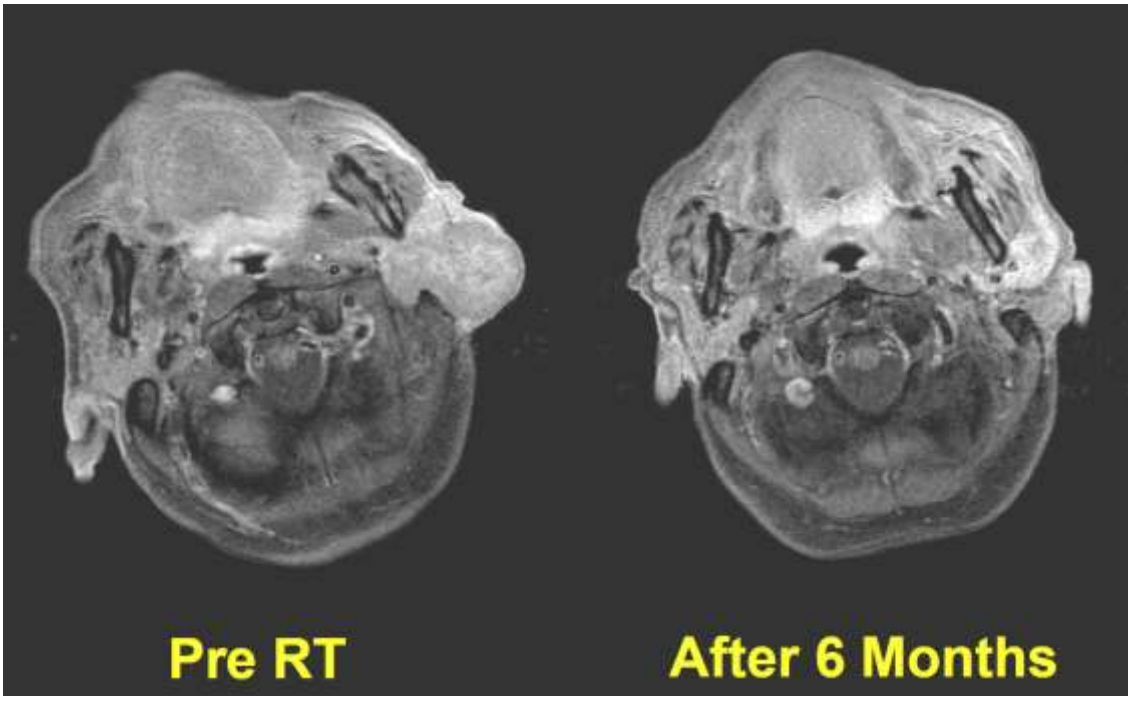


Figure 8: Tumour of the left parotid gland treated with carbon ion therapy at the NIRS (Chiba, Japan); outcomes shown in Table VIII

Table VIII

Indication: Salivary gland carcinomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Laramore 1993	Neutrons (13) vs photons (12)	**Prospective randomised trial**	10-yr LRC(n): 56% 10-yr LRC(p): 17%	10-yr OS(n):15% 10-yr OS(p):25%
Chen 2006	Photons (45)	Retrospective	5-yr LC: 70% 10-yr LC: 57%	5-yr OS: 70% 10-yr OS: 46%
Terhaard 2005	Photons (40)	Retrospective	5-yr LC for dose ≥ 66 Gy: 50% (n=20) 5-yr LC for dose < 66 Gy: 0%	N/A
Mizoe 2007	**Carbon ions (31)**	**Prospective phase II**	**5-yr LC: 80.4%**	**5-yr OS: 64.1%**
Weighted mean difference in 5-year local control rates between carbon ions (80.4%) and photons (56.5%) = +23.9%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available

References:

Bittner et al. *"Treatment of locally advanced adenoid cystic carcinoma of the trachea with neutron radiotherapy". Int. J. Radiation Oncology Biol. Phys. 2008;72(2):410–414.*
Brackrock et al. *"Neutron therapy, prognostic factors and dedifferentiation of adenoid cystic carcinomas (ACC) of salivary glands". Anticancer research, 2006;25:1321–1326.*
Chen et al. *"Long-term outcome of patients treated by radiation therapy alone for salivary gland carcinomas". Int. J. Radiation Oncology Biol. Phys. 2006;66(4):1044–1055.*

Daly et al. *"Intensity-modulated radiation therapy for malignancies of the nasal cavity and paranasal sinuses". Int. J. Radiation Oncology Biol. Phys. 2007;67(1):151–157.*
Dirix et al. *"Post-operative intensity-modulated radiotherapy for malignancies of the nasal cavity and paranasal sinuses". Radiotherapy and Oncology. 2007;85:385–391.*
Douglas et al. *"Treatment of locally advanced adenoid cystic carcinoma of the head and neck with neutron radiotherapy". Int. J. Radiation Oncology Biol. Phys. 2000;46(3)551–557.*
Duthoy et al. *"Postoperative intensity-modulated radiotherapy in sinonasal carcinoma". Cancer. 2005;104:71–82.*
Fukumitsu et al. *"Outcome of T4 (International Union Against Cancer Staging System, 7th edition) or Recurrent Nasal Cavity and Paranasal Sinus Carcinoma Treated with Proton Beam". Int. J. Radiation Oncology Biol. Phys. 2011 [epub ahead of print].*
Hasegawa et al. *"Carbon ion radiotherapy for malignant head-and-neck tumors". Proceedings of NIRS-ETOILE 2nd Joint Symposium 2011 on Carbon Ion Radiotherapy, November 2011: 18–23*
Laramore et al. *"Neutron versus photon irradiation for unresectable salivary gland tumors: Final report of an RTOG-MRC randomized clinical trial". Int. J. Rad. Oncology Biol. Phys. 1993;27:235–240.*
Madani, et al. *« Intensity-modulated radiotherapy for sinonasal tumors: GHENT university hospital update». Int. J. Radiation Oncology Biol. Phys. 2009;73:424–432.*
Mizoe et al. *"PTCOG 46 Educational workshop Session IV: Clinical Head & Neck". 2007*
Mizoe et al. *"Results of carbon ion radiotherapy for head and neck cancer". Radiother Oncol 2012 [epub ahead of print].*
Mizoe et al. *"Head and neck tumors". Proceedings of NIRS-ETOILE Joint symposium on carbon ion radiotherapy, March 2009: 32–37.*
Pommier et al. *"Proton beam radiation therapy for skull base adenoid cystic carcinoma". Arch otolaryngol head neck surg, 2006;132:1242–1249.*
Prott et al. *"Results of fast neutron therapy of adenoid cystic carcinoma of the salivary glands". Anticancer Research, 2000;20:3743–3750.*
Schulz-Ertner D et al. *"Feasibility and toxicity of combined photon and carbon ion radiotherapy for locally advanced adenoid cystic carcinomas". Int J Radiat Oncol Biol Phys. 2003; 56(2):391–398.*
Schulz-Ertner D et al. *"Results of carbon ion radiotherapy in 152 patients". Int J Radiat Oncol Biol Phys. 2004; 58(2):631–640.*
Schulz-Ertner D et al. *"Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques". Cancer. 2005;104:338–44.*
Terhaard et al. *"The role of radiotherapy in the treatment of malignant salivary gland tumors". Int. J. Radiation Oncology Biol. Phys. 2005;61(1):103–111.*
Truong et al. *"Proton radiation therapy for primary sphenoid sinus malignancies: treatment outcome and prognostic factors". Head Neck. 2009;31:1297–308.*
Zenda et al. *"Proton beam therapy for unresectable malignancies of the nasal cavity and paranasal sinuses". Int. J. Radiation Oncology Biol. Phys. 2011;81:1473–8.*

<u>Malignant Mucosal Melanomas:</u>

A Japanese phase II trial (protocol 9602) recruited 102 patients with histologically-confirmed mucosal melanomas that were measurable and located in the head and neck. The trial began in April 1997 and consisted of local carbon ion therapy alone, with no associated first-line chemotherapy. The dose administered was either 57.6 GyE or 64.0 GyE in 16 fractions over 4 weeks. The local control and 5-year survival rates were 74% and 36% respectively.

Another Japanese phase II trial (protocol 0007) included 103 patients with mucosal melanoma. These patients presented satisfactory overall condition (Karnofsky Score between 70% and 100%) and were therefore able to receive both radiotherapy and chemotherapy. The mean age was 62 years (26–79 years). The population included 56 women and 47 men. Most of the tumours were located in the nasal cavity or paranasal sinuses; a few were located in the oral cavity, ocular orbit or pharynx. The dose administered was 57.6 GyE in 16 fractions over 4 weeks. Chemotherapy (DAV) was administered

concomitantly to radiotherapy in 96 patients. Outcomes were complete response in 22 patients, regression in 47 patients and stability in 35 patients; no cases of progression were described. Acute reactions were limited to grade 3 skin toxicity and 21 cases of grade 3 mucosal toxicity. No grade 3 late toxicity was observed. In the group of patients who received chemotherapy plus radiotherapy (n = 96), the 5-year local control and survival rates were 81% and 58% respectively. Survival was significantly correlated with tumour size (p <0.005): 5-year survival was 68% with gross tumour volumes less than 60 cc (60 patients), and 24% with volumes greater than 60 cc (15 patients).

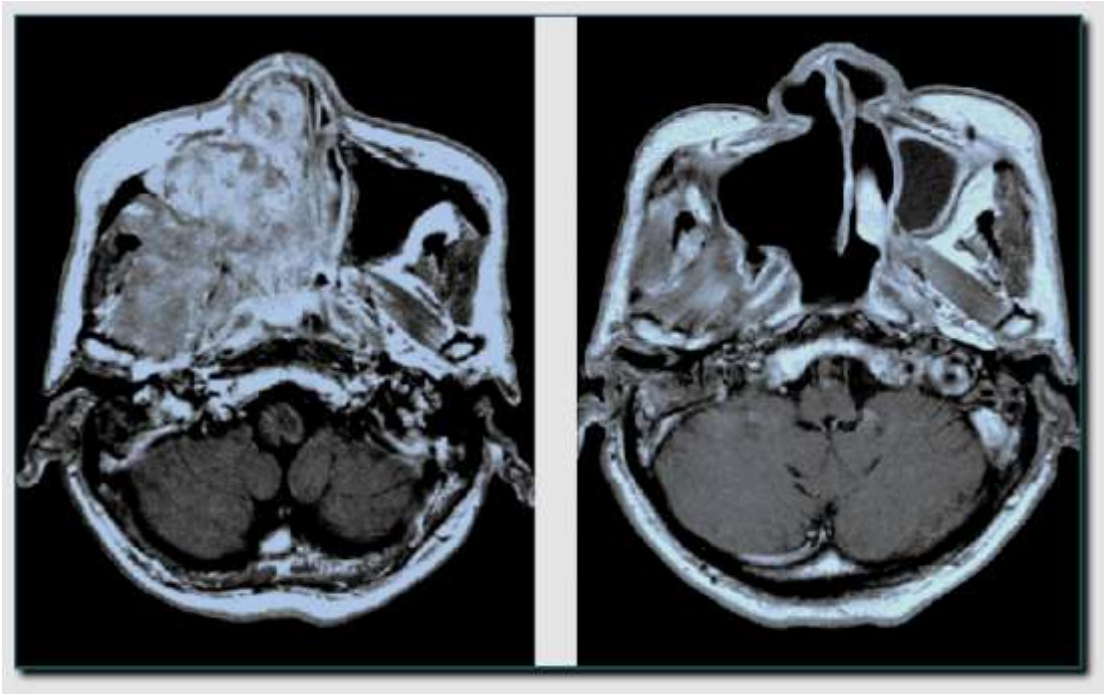


Figure 9: Example of malignant melanoma of the nasal fossae treated at the NIRS (Chiba, Japan); outcomes shown in Table IX

Table IX

Indication: Head and neck mucosal melanomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Wada 2004	Photons (31)	Retrospective	3-yr CSS*: 33%	N/A
Gilligan 1991	Photons (28)	Retrospective	5-yr LC: 61% 5-yr DFS: 55%	5-yr OS: 18%
Krengli 2006	Surgery + photons (42)	Retrospective	5-yr DFS: 28%	5-yr OS: 28%
Teman 2005	Surgery + photons (39)	Retrospective	5-yr LC: 34%	5-yr OS: 18%
Tsunemoto 2009	Neutrons (20)	Retrospective	N/A	5-yr OS: 15.4% 10-yr OS: 7.7%
Zenda 2011	Protons (14)	Retrospective	2-yr PFS: 43.7%	3-yr OS: 58%
Yanagi 2009	Carbon ions (72)	Prospective phase II	5-yr LC: 84.1%	5-yr OS: 27.0%
Jingu 2011	Carbon ions + chemotherapy (37)	retrospective	3-yr LC: 81.1%	3-yr OS: 65.3%

Indication: Head and neck mucosal melanomas					
Author, year		Treatment (number	Type of study	Efficacy	
Hasegawa 2011 NIRS	**Protocol 9602†**	**Carbon ions (102)**	**Prospective phase II**	**5-yr LC: 79%**	**5-yr OS: 35%**
	Protocol 0007†	**Carbon ions + concomitant chemotherapy (96/103)**		**5-yr LC: 81%**	**5-yr OS: 58%**
Weighted mean difference in 5-year local control rates between carbon ions alone (81.1%) and photons ± surgery (45.3%) = +35.8%					

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
*CSS: Cause-specific survival
†Update provided at the 2nd NIRS-ETOILE Joint Symposium 2011 in Lyon, France.

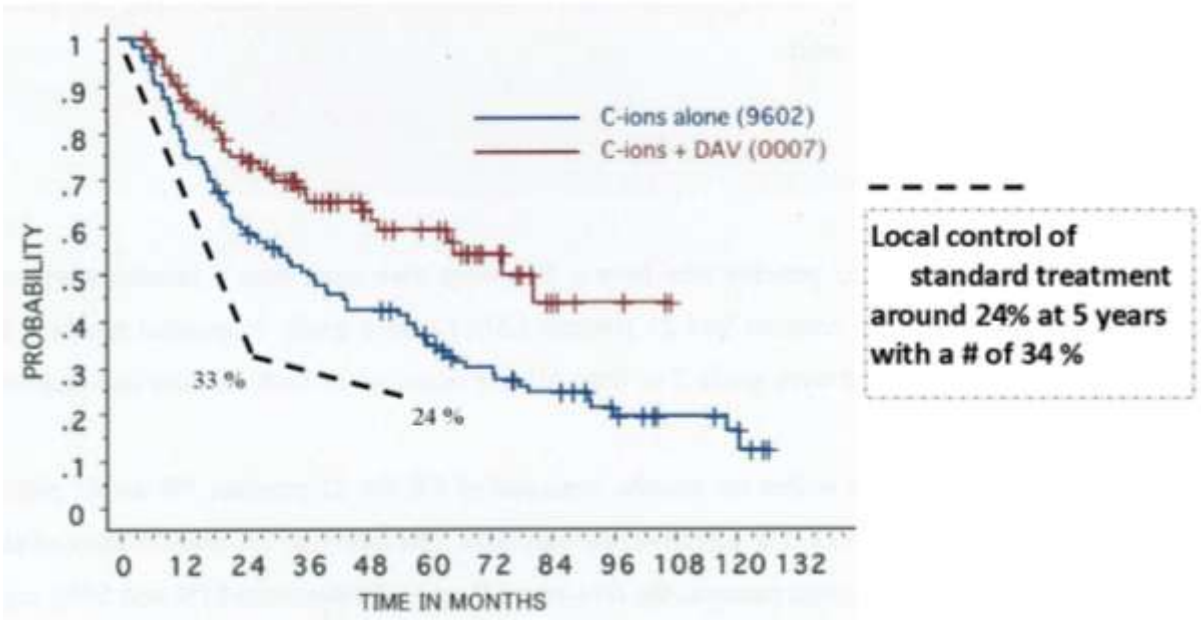


Figure 10: Overall survival of malignant mucosal melanoma patients treated with carbon ions or carbon ions + chemotherapy at the NIRS (Chiba, Japan) versus carbon-free treatments; outcomes shown in Table IX

References:

Gilligan et al. *"Radical radiotherapy for 28 cases mucosal melanoma in the nasal cavity and sinuses". Br J Radiol. 1991;64:1147–50.*
Hasegawa et al. *"Carbon ion radiotherapy for malignant head-and-neck tumors". Proceedings of NIRS-ETOILE 2nd Joint Symposium on carbon ion radiotherapy, November 2011:18–23.*
Jingu et al. *"Malignant mucosal melanoma treated with carbon ion radiotherapy with concurrent chemotherapy: prognostic value of pretreatment apparent diffusion coefficient (ADC)". Radiother Oncol. 2011;98:68–73.*
Krengli et al. *"Radiotherapy in the treatment of mucosal melanoma of the upper aero-digestive tract. A rare cancer network study". Int. J. Radiation Oncology Biol. Phys. 2006;65(3):751–9.*
Mizoe et al. *"Results of carbon ion radiotherapy for head and neck cancer". Radiother Oncol 2012 [epub ahead of print].*
Temam et al. *"Postoperative radiotherapy for primary mucosal melanoma of the head and neck". Cancer. 2005;103:313–9.*

Tsunemoto et al. *"Characteristics of malignant melanoma cells in the treatment with fast neutrons". Pigment Cell Res. 1989;2:372–8.*
Wada et al. *"A multi-institutional retrospective analysis of external radiotherapy for mucosal melanoma of the head and neck in northern Japan". Int. J. Radiation Oncology Biol. Phys. 2004;59(2):495–500.*
Yanagi et al. *"Mucosal malignant melanoma of the head and neck treated by carbon ion radiotherapy". Int. J. Radiation Oncology Biol. Phys. 2009;74:15–20.*
Zenda et al. *"Proton beam therapy as a nonsurgical approach to mucosal melanoma of the head and neck: A pilot study". Int. J. Radiation Oncology Biol. Phys. 2011;81:135–139.*

Chordomas at the base of the skull:

The main experience of carbon ion radiotherapy specific to chordomas at the base of the skull has been gained at the experimental facility of Darmstadt, in Germany. A total of 96 patients with chordomas at the base of the skull received radiation at a dose of 60 GyE in 20 fractions. The first 44 patients were recruited in a phase I/II prospective trial, and 52 patients were treated subsequently according to the same protocol. Radiotherapy was provided as initial treatment to 59 patients (61.5%), and a recurrence in 37 cases (38.5%). The median follow-up time was 31 months. The actuarial 3-year and 5-year local control rates were 80.6% and 70% respectively; the 3-year and 5-year overall survival rates were 91.8% and 88.5% respectively. Five cases of late toxicity of grade 3 or above were observed: 4 optic nerve neuropathies and 1 case of necrosis. In this series an increase of the radiation dose to above 60 GyE was associated with a significant increase in the local control rate ($p = 0.029$), with 5-year local control increasing from 63% to 100%. Patients receiving radiation as initial treatment had a significantly higher probability of local control than patients being treated for a recurrence ($p = 0.01$).

The results for the 44 patients in the phase I/II trial had been published in advance. These patients had been recruited between September 1998 and December 2001. The radiation dose was 60 GyE in 20 fractions of 3 GyE. Median follow-up time is currently approximately 46 months. The 3-year local control rate was 87%, with an overall survival rate of 89%. The update at 5 years gives corresponding figures of 88% and 87% respectively. Three cases of grade 2 late toxicity were observed, and no cases of grade 3 late toxicity. The results for patients treated for a chordoma at the base of the skull can be found in several publications. An update was provided by Koto M et al at the NIRS-ETOILE 2nd Joint Symposium in November 2011 in Lyon, France.

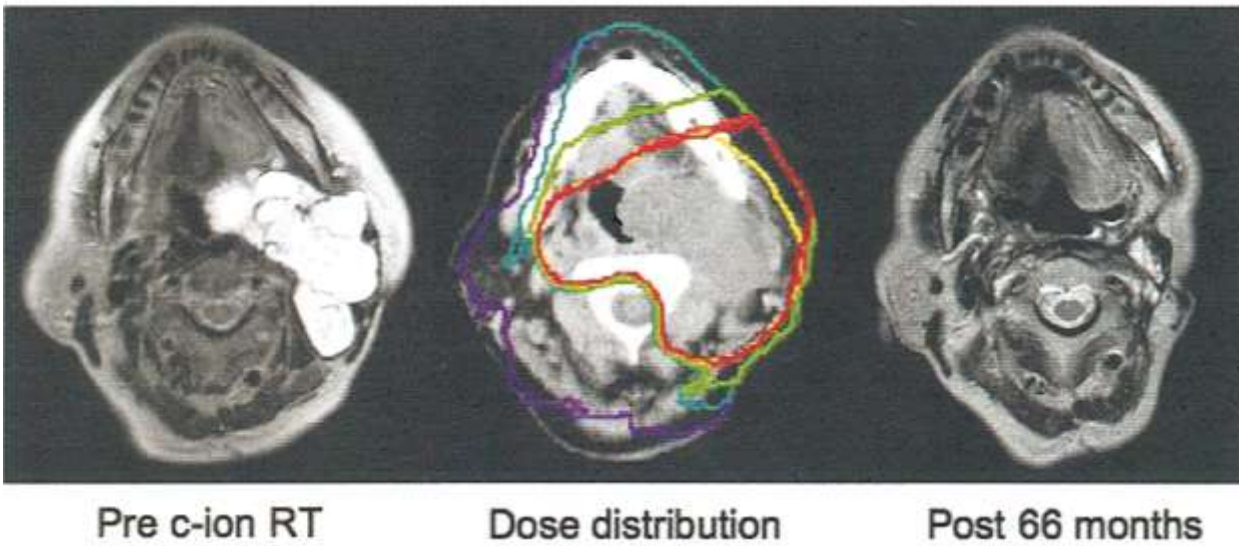


Figure 11: Example of a recurrent chordoma at the base of the skull following surgery, treated with carbon ion therapy at the NIRS (Chiba, Japan); outcomes shown in Table X. Isodoses: red = 96%, orange = 90%, green = 50%, cyan = 30%, violet = 10%; target outlined in yellow.

In addition, in its series of sarcomas the NIRS highlights a group of 126 patients with chordomas that had developed outside the base of the skull and were essentially treated with 70.4 GyE (16 fractions of 4.4 GyE over 4 weeks). The group yielded a 5-year local control rate of 89% and a 5-year overall survival rate of 85%. This demonstrates carbon ion therapy's high efficacy in this disease, even outside the base of the skull.

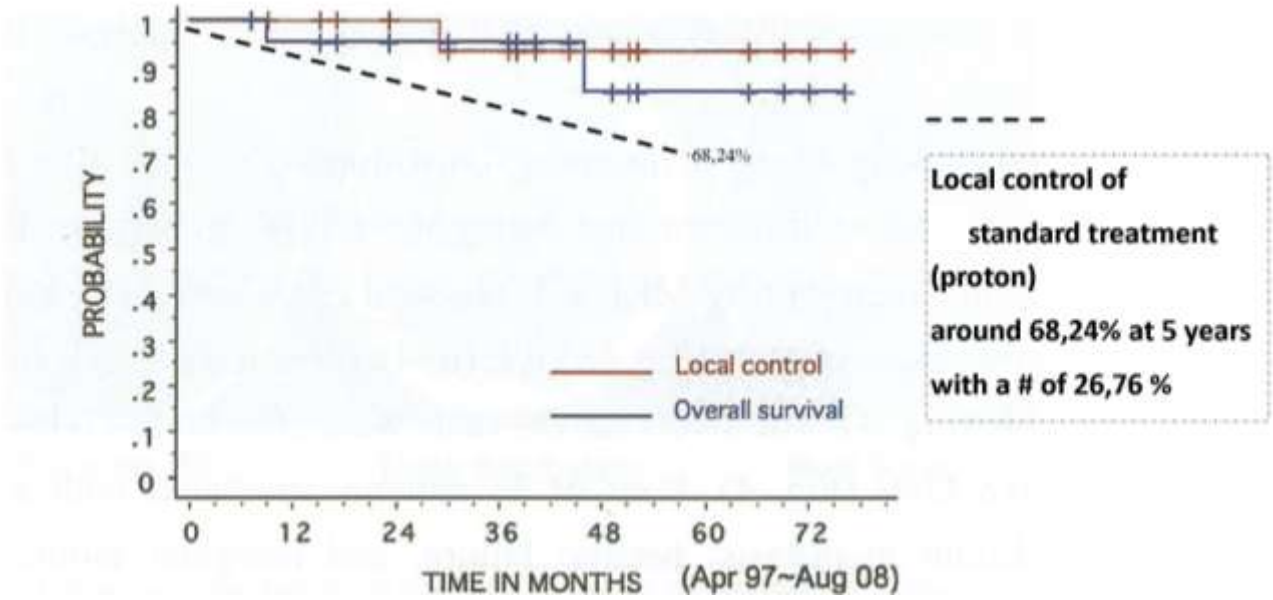


Figure 12: Local control and overall survival for 21 chordomas irradiated at a dose of 60.8 GyE at the NIRS (Chiba, Japan) versus carbon-free treatments; outcomes shown in Table X

Table X

Indication: Skull base chordomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Ares 2009	Protons (43)	42	5-yr LC: 81%	5-yr OS: 62%
Weber 2005	Protons (18)	Retrospective	3-yr LC: 87.5%	N/A
Noel 2005	Protons + photons (99)	Retrospective	4-yr LC: 53.8%	5-yr OS: 80.5%
Munzenrider 1999	Protons + photons (290)	Retrospective	5-yr LRFS*: 73%	5-yr OS: 80%
Hug 1999	Protons + photons (33)	Retrospective	5-yr LC: 59%	5-yr OS: 79%
Fuji 2011	**Protons (8)**	**Retrospective**	**3-yr LC: 100%**	**3.5-yr OS: 100%**
Schulz-Ertner 2007	**Carbon ions (96)**	**Phase I/II + retrospective**	**5-yr LC: 70%**	**5-yr OS: 88.5%**
Mizoe 2009	**Carbon ions (33)**	**Pilot + phase I/II + phase II**	**5-yr LC: 85.1% 10-yr LC: 63.8%**	**5-yr OS: 87.7% 10-yr OS: 67%**
Koto 2011† NIRS	**Carbon ions (44)**	**Phase II**	**5-yr LC: 88%**	**5-yr OS: 87%**
Weighted mean difference in 5-year local control rates between carbon ions (77.5%) and protons ± photons (68.3%) = +9.2%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
*LRFS: Local recurrence-free survival
†Update provided at the 2nd NIRS-ETOILE Joint Symposium 2011 in Lyon, France.

References:

Ares et al. *"Effectiveness and Safety of Spot Scanning Proton Radiation Therapy for Chordomas and Chondrosarcomas of the Skull Base: First Long-Term Report". Int J Radiat Oncol Biol Phys. 2009 Apr 20 [epub ahead of print].*
Fuji et al. *"Feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base". Skull Base. 2011;21:201–206.*
Hug MD et al. *"Proton radiation therapy for chordomas and chondrosarcomas of the skull base". J Neurosurg 1999;91:432–439.*
Kamada T et al. *"Carbon ion therapy in bone and soft tissue sarcomas" Proceedings of NIRS-ETOILE Joint symposium on carbon ion radiotherapy, March 2009: 50–56.*
Koto M et al. *"Carbon ion radiotherapy for skull base and paracervical tumors" Proceedings of NIRS-ETOILE 2nd Joint Symposium on carbon ion radiotherapy, November 2011: 12–17.*
Mizoe et al. *"Carbon ion radiotherapy for skull base chordoma". Skull Base. 2009;19:219–24.*
Munzenrider JE et al. *"Proton therapy for tumors of the skull base". Strahlenther Onkol 1999 June;175 Suppl 2:57–63.*
Noel G et al. *"Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams". Acta Oncologica, 2005;44:700–708.*
Schulz-Ertner D et al. *"Results of carbon ion radiotherapy in 152 patients". Int J Radiat Oncol Biol Phys. 2004; 58(2):631–640.*
Schulz-Ertner D et al. *"Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas of the skull base: Results in 67 patients" Strahlentherapie und Onkologie, 2003;179(9):598–605.*
Schulz-Ertner D et al. *"Acute radiation-induced toxicity of heavy ion radiotherapy delivered with intensity modulated pencil beam scanning in patients with base of skull tumors" Radiother Oncol, 2002;64:189–195.*
Schulz-Ertner D et al. *"Carbon ion radiotherapy for chordomas and low-grade chondrosarcomas-current status of clinical trials at GSI" Radiother Oncol, 2004;73(suppl 2):S53–6.*
Schulz-Ertner D et al. *"Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions" Int. J. Radiation Oncology Biol. Phys., 2002;53(1):36–42.*
Schulz-Ertner D et al. *"Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas" Int. J. Radiation Oncology Biol. Phys. 2007;68(2):449–457.*
Weber D et al. *"Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: The Paul Scherrer Institut experience". Int. J. Radiation Oncology Biol. Phys. 2005;63(2):401–409.*

<u>Sarcomas of the axial skeleton (excluding the skull) and soft-tissues (chordomas, osteosarcomas, chrondrosarcomas, histiocytic fibrosarcomas, Ewing's sarcomas):</u>

The CHIBA facility in Japan published an initial phase I/II dose-ranging trial to evaluate the tolerance and efficacy of carbon ion therapy in the treatment of inoperable sarcomas. A total of 57 patients with 64 sarcomas considered inoperable (15 osteosarcomas, 11 chordomas, 6 chrondrosarcomas, 18 soft-tissue sarcomas) were recruited. The tumours were locally advanced (median volume 560 ml) and mostly located in the pelvis and spinal or paraspinal region (21 tumours). Carbon ion radiotherapy was performed in 16 fractions over 4 weeks, with doses ranging from 52.8 GyE to 73.6 GyE. For the patient population as a whole the local control rates were 73% at 3 years and 63% at 5 years, but for those with radiation doses above 64 GyE it was 84%. The 3-year actuarial overall survival rate was 46%; the 5-year figure was 37%. Six patients with superficial tumours presented a grade 3 skin toxicity, and seven others grade 2 peripheral neuropathy.

This initial trial was followed by a phase II trial. A total of 495 patients with 514 soft-tissue or skeletal sarcomas were recruited. The radiation dose was 70.4 GyE for 376 lesions, 73.6 GyE for 10 lesions, 67.2 GyE for 70 lesions and 64 GyE for 32 lesions. The local control rate was 85% at 2 years and 69% at

5 years. The 2-year and 5-year overall survival rates were 79% and 59% respectively. 2% of patients experienced grade 3–4 acute skin toxicity; one patient presented grade 4 delayed skin toxicity, and six patients grade 3 delayed skin toxicity. One patient presented grade 2 delayed spinal neurological toxicity.

Table XI

Indication: Cervical spine chordomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Munzenrider 1999	Photon + protons (85)	Retrospective	5-yr LRFS: 69%	5-yr OS: 80%
No data on carbon ion radiotherapy were published.				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available

Table XII

Indication: Sacral chordomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Breteau 1998	Neutrons (13)	Retrospective	4-yr LC: 61%	4-yr OS: 54%
Pack 2006	Surgery + protons (+/- photons) (45)	Retrospective	5-yr LC: 71.7% 10-yr LC: 57.5%	5-yr OS: 82.5% 10-yr OS: 62.5%
Imai 2011†	**Carbon ions (95)**	**Phase I/II + II**	**5-yr LC: 88%**	**5-yr OS: 86%**
Weighted mean difference in 5-year local control rates between carbon ions (88%) and non-carbon treatments (68%) = +20%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
†Update provided at the 2nd NIRS-ETOILE Joint Symposium 2011 in Lyon, France.

Table XIII

Indication: Skull base chondrosarcomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Weber 2005	Protons (11)	Prospective observational study	3-yr LC: 100%	N/A
Noel 2004	Protons + photons (26)	Retrospective	3-yr LC: 91%	3-yr OS: 95.8% 4-yr OS: 86.3%
Munzenrider 1999	Protons + photons (229)	Retrospective	5-yr LRFS*: 73%	5-yr OS: 91%
Hug 1999	Protons + photons (25)	Retrospective	5-yr LC: 75%	5-yr OS: 100%
Fuji 2011	**Protons (8)**	**Retrospective**	**3-yr LC: 86%**	**3.5-yr OS: 100%**
Schulz-Ertner 2007	**Carbon ions (54)**	**Phase I/II+ retrospective**	**4-yr LC: 89.8%**	**5-yr OS: 98.2%**
Weighted mean difference in 5-year local control rates between carbon ions (80%?) and protons ± photons (73.2%) = +7%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
*LRFS: Local recurrence-free survival

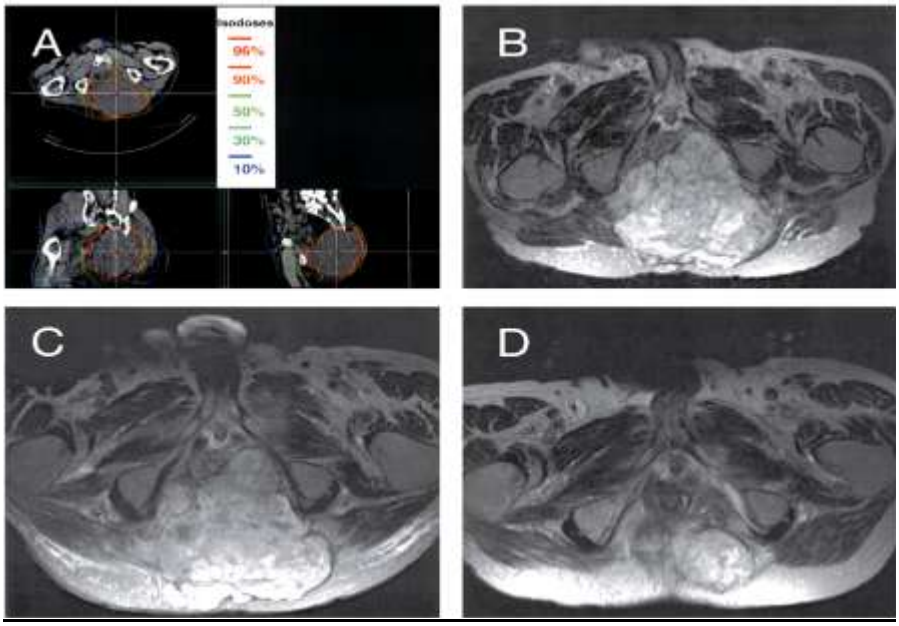


Figure 13: Example of sacral chordoma on MRI (B) before treatment, (C) 4 months after carbon ion therapy and (D) 18 months after treatment, showing gradual regression, NIRS (Chiba, Japan); outcomes shown in Table XII

Table XIV

Indication: Cervical spine chondrosarcomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Munzenrider 1999	Photon + proton (17)	Retrospective	5-yr LRFS: 54%	5-yr OS: 48%
No data on carbon ion radiotherapy were published.				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; LRFS: Local recurrence-free survival

Table XV

Indication: soft-tissue sarcomas (R2, recurrent or unresectable)				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Kepka 2005	Photons (112)	Retrospective	5-yr LC: 45%	5-yr OS: 35%
Schwartz 2001	Neutrons, RT, brachytherapy (73)	Retrospective	4-yr LRFS: 61%	N/A
Shmitt 1989	Neutrons, RT (221)	Retrospective	5-yr LC: 58.4% 5-yr DFS: 25.5%	N/A
Weber 2007	Protons, RT (13)	Retrospective	4-yr LC: 74.1%	N/A
NIRS 2009*	**Carbon ions (57) 52.8–73.6 GyE**	**Phase I/II**	**5-yr LC: 63%**	**5-yr OS: 37%**
	Carbon ions (331) 64–73.6 GyE	**Phase II**	**5-yr LC: 79%**	**5-yr OS: 57%**
Weighted mean difference in 5-year local control rates between carbon ions (76.6%) and non-carbon treatments (55.5%) = +21.1%				

*This study included patients with locally advanced and/or inoperable bone and soft-tissue sarcomas.
LC: Local control; LRFS: Local recurrence-free survival; DFS: Disease-free survival; OS: Overall survival; N/A: Not available

Table XVI

Indication: Bone and soft-tissue sarcomas, global results				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Imai 2011[†]	**Carbon ions (495) 70.4 GyE**	**Phase II**	**5-yr LC: 69% 10-yr LC: 56%**	**5-yr OS: 59% 10-yr OS: 44%**
Jingu 2012	**Carbon ions (27) 70.4 GyE/16 fr**	**Prospective**	**3-yr LC: 91.8%**	**3-yr OS: 74.1%**
Sugahara 2012	**Carbon ions (27) 52.8 GyE–70.4 GyE/16 fr**	**Phase I/II**	**5-yr LC: 76%**	**5-yr OS: 56%**

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
[†]Update provided at the 2nd NIRS-ETOILE Joint Symposium 2011 in Lyon, France.

Table XVII

Indication: Osteosarcomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Matsunobu 2012	**Carbon ions (78) 70.4 GyE/16 fr**	**Retrospective**	**5-yr LC: 62%**	**5-yr OS: 33%**

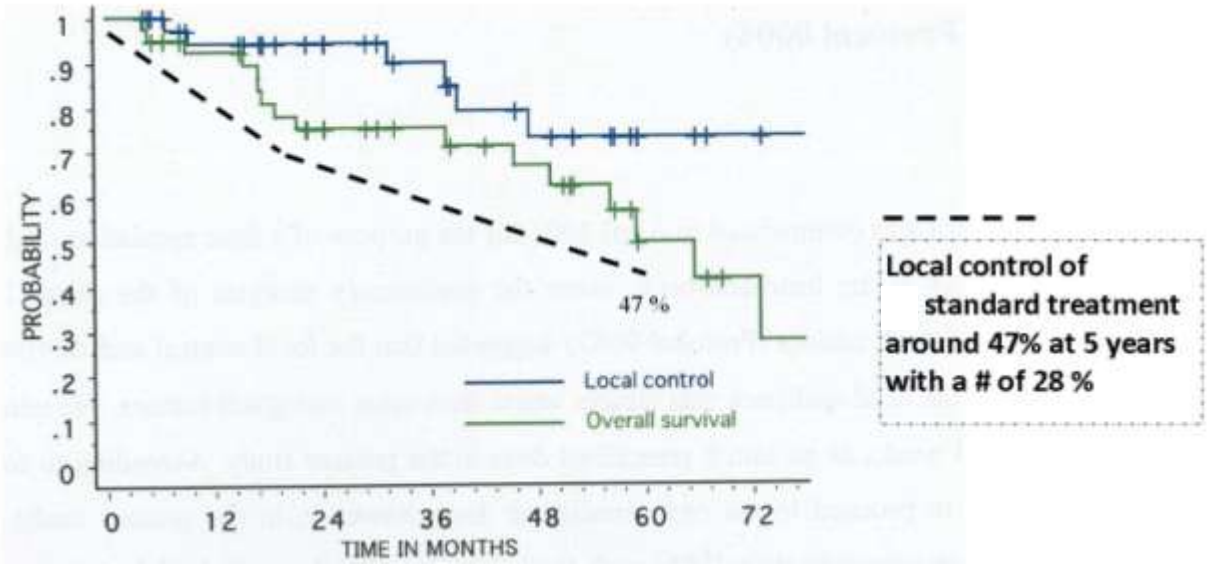


Figure 14: Local control and overall survival rates of inoperable bone and soft-tissue sarcomas receiving carbon ion therapy at the NIRS (Chiba, Japan); outcomes shown in Tables XIII–XVI

References:

Breteau N et al. *"Sacrococcygeal chordomas: potential role of high LET therapy". Recent Results Cancer Res 1998; 150: 148–55.*
Fuji et al. *"Feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base". Skull Base. 2011;21:201–206.*
Hug MD et al. *"Proton radiation therapy for chordomas and chondrosarcomas of the skull base". J Neurosurg 1999;91:432–439.*
Imai R et al. *"Carbon ion radiotherapy for sacral chordomas". Br J Radiol 2011 [epub ahead of print].*
Imai R et al. *"Carbon ion radiotherapy for unresectable sacral chordomas". Clinical Cancer Research 2004;10:5741–5746.*

Imai R et al. *"Effect of carbon ion radiotherapy for sacral chordoma: results of Phase I-II and phase II clinical trials". Int. J. Radiation Oncology Biol. Phys. 2010;75:1470–6.*
Imai R et al. *"Carbon ion radiotherapy for bone and soft tissue sarcomas" Proceedings of NIRS-ETOILE 2nd Joint Symposium on carbon ion radiotherapy, November 2011: 38-45.*
Iwata et al. *"Efficacy of carbon-ion radiotherapy and high-dose chemotherapy for patients with unresectable Ewing's sarcoma family of tumors". Int J Clin Oncol 2012 [epub ahead of print].*
Jingu et al. *"Carbon ion radiation therapy improves the prognosis of unresected adult bone and soft-tissue sarcoma of the head and neck". Int. J. Radiation Oncology Biol. Phys. 2012;82(5):2125–2131.*
Kamada T et al. *"Carbon ion therapy in bone and soft tissue sarcomas". Proceedings of NIRS-ETOILE Joint symposium on carbon ion radiotherapy, March 2009: 50–56.*
Kamada T et al. *"Efficacy and safety of carbon ion radiotherapy in bone and soft tissue sarcomas" J Clin Oncol 2002; 20: 4461–4471.*
Kepka et al. *"Results of radiation therapy for unresected soft-tissue sarcomas". Int. J. Radiation Oncology Biol. Phys. 2005;63(3):852–859.*
Matsunobu et al. *"Impact of carbon ion radiotherapy for unresectable osteosarcoma of the trunk" Cancer 2012; 118: 4555–4563.*
Munzenrider JE et al. *"Proton therapy for tumors of the skull base". Strahlenther Onkol 1999 June;175 Suppl 2:57–63.*
Noel G et al. *"Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas". Neurosurgery 2004;55:1252–1262.*
Park et al. *"Sacral chordomas: Impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor". Int. J. Radiation Oncology Biol. Phys. 2006;65(5):1514–1521.*
Schmitt et al. *"The role of neutrons in the treatment of soft tissue sarcomas". Cancer 1989;64:2064–8.*
Schulz-Ertner D et al. *"Carbon ion radiotherapy of skull-base chondrosarcomas". Int. J. Radiation Oncology Biol. Phys. 2007;67(1):171–177.*
Schwartz et al. *"Fast neutron radiotherapy for soft tissue and cartilaginous sarcomas at high risk for local recurrence". Int. J. Radiation Oncology Biol. Phys. 2001;50:449–65.*
Sugahara et al. *"Carbon ion therapy for localized primary sarcoma of the extremities: results of a phase I/II trial" Radiother Oncol. 2012; 105: 226–231.*
Weber D et al. *"Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: The Paul Scherrer Institut experience". Int. J. Radiation Oncology Biol. Phys. 2005;63(2):401–409.*
Weber D et al. *"Spot scanning proton therapy in the curative treatment of adult patients with sarcoma: The Paul Scherrer Institute experience". Int. J. Radiation Oncology Biol. Phys. 2007,69(3):865–871.*
Zhang et al. *"[^{11}C]Methionine positron emission tomography and survival in patients with bone and soft-tissue sarcomas treated by carbon ion radiotherapy" Clinical Cancer Research. 2004; 10: 1764–1772.*

<u>Local, unresectable recurrences of rectal cancer:</u>

NIRS is conducting a phase I/II dose-ranging study of carbon ion therapy in patients with pelvic local recurrences of rectal adenocarcinomas that have not previously received radiotherapy. Over 100 patients (n = 140) were recruited between 2001 and February 2010 (study still ongoing), with 148 sites of tumour recurrence. Recurrences were presacral in 48% of cases, in the lateral region of the pelvis in 28%, perineal in 16% and at the colorectal anastomosis in 8%. All patients received carbon ion radiotherapy. The total dose ranged from 67.2 GyE to 73.6 GyE, administered in 16 fractions over 4 weeks (4.2 GyE to 4.6 GyE per fraction).

The 3-year local control rate in patients treated at 73.6 GyE (n = 111) was 95.2%; the 5-year figure was 95.2%. Dose-ranging was halted at this dose. The median survival time of patients treated at this dose was 54 months (7–65 months), and the overall survival rates were 86% at 2 years, 73.5% at 3 years and 42.3% at 5 years. Tolerance was good, with no acute toxicity of grade 3 or above.

A study involving recurrent rectal cancers that had previously received initial radiotherapy is ongoing. The results for the first 23 patients were presented at the 2nd NIRS-ETOILE Joint Symposium in November 2011 in Lyon, France (see Table XVII).

Table XVIII

Indication: Recurrent rectal cancers				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Palmer 2006	ChemoRT: photons (48)	Population-based study	N/A	3-yr OS: 11%
Valentini 2006	ChemoRT: photons* (59)	Prospective phase II	5-yr LC: 38.8% 5-yr DFS: 29.2%	N/A
Yamada 2011†	**Carbon ions (111/140)**	**Prospective Phase I/II**	**3-yr LC: 95.2% (73.6 GyE)** **5-yr LC: 95.2% (73.6 GyE)**	**3-yr OS: 73.5% (73.6 GyE)** **5-yr OS: 42% (73.6 GyE)**
Yamada 2011†	**Carbon ions (Repeat irradiation*) (23)**	**Prospective Phase I/II**	**1-yr DFS: 71%** **3-yr DFS: 51%**	**1-yr OS: 83%** **3-yr OS: 65%**
Weighted mean difference in 5-year local control rates between carbon ions (95%) and chemoRT (39%) = +56%				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; N/A: Not available
*Patients were previously irradiated during initial treatment for their disease.
†Update provided at the 2nd NIRS-ETOILE Joint Symposium 2011 in Lyon, France.

References:

Palmer G et al. *"A Population-Based Study on the Management and Outcome in Patients with Locally Recurrent Rectal Cancer", Annals of Surgical Oncology 14(2):447–454, 2006.*
Valentini et al. *"Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study". Int. J. Radiation Oncology Biol. Phys. 2006;64(4):1129–1139.*
Yamada S et al. *"Carbon ion radiotherapy for patients with locally recurrent rectal cancer", Proceedings of NIRS-ETOILE 2nd Joint Symposium 2011 on carbon ion radiotherapy November 2011:54–59.*
Yamada S et al. *"Carbon-ion therapy for patients with locally recurrent rectal cancer and pancreas cancer", NIRS 2006.*
Yamada S et al. *"Carbon ion therapy for patients with locally recurrent rectal cancer" Proceedings of NIRS-ETOILE Joint Symposium on carbon ion radiotherapy, March 2009: 64–71.*

Single large hepatocellular carcinomas:

The NIRS has acquired a great deal of experience in carbon ion therapy for hepatocellular carcinoma. Hepatocellular carcinoma presents differently in Japan (post-hepatic liver) and in France (cirrhotic liver, usually alcoholic). Clinical trials were conducted between 1995 and 2005, involving 193 patients with hepatocellular carcinoma. The first two phase I/II studies where dose-ranging studies with 10% dosing increments, exploring a gradual reduction in the number of fractions from 12 to 8 and then 4. These studies established that the treatment was effective and well tolerated. A third phase II study was conducted, with a standardised radiotherapy regimen: 52.8 GyE in four fractions. A total of 116 patients were treated according to this regimen for lesions divided equally between primary tumours and recurrences and presented with a median diameter of 4 cm (1.2–12 cm) with good initial tolerance and a 5-year local control rate of 95%.

A fourth study was then conducted between 2003 and 2005, with a two-fraction regimen over two days, increasing from 32 GyE to 38.8 GyE; 36 patients were enrolled. Since 2005 this protocol has become the NIRS's standard regimen for its routine care. To date there have no deaths due to toxicity with this disease, or any serious side effects.

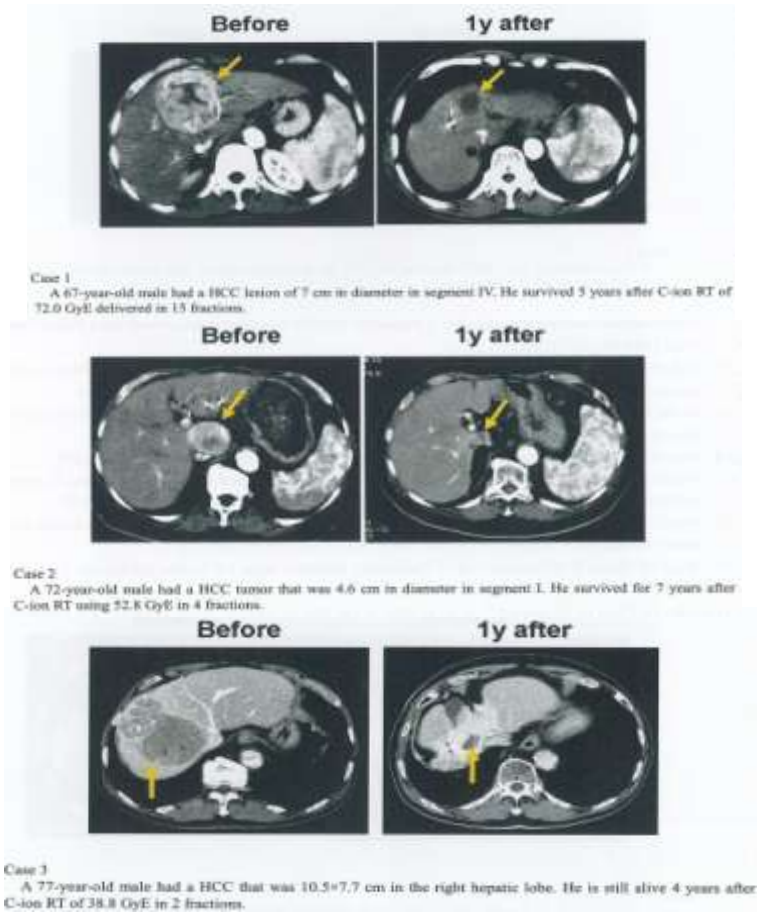


Figure 15: Three cases of hepatocellular carcinoma treated with carbon ion therapy at the NIRS (Chiba, Japan); outcomes shown in Table XVIII

Table XIX

Indication: Hepatocellular carcinomas				
Author, year	Treatment (number of patients)	Type of study	Efficacy	
			LC/LRC/DFS	OS
Li 2003	TACE + 3DRT(45)	Prospective study	3-yr PDFS: 42.4%	3-yr OS: 22.6%
Yamada 2003	TACE + 3DRT(19)	Prospective study	N/A	2-yr OS: 10.2%
Bush 2004	Protons (34)	Phase II	2-yr LC: 75%	2-yr OS: 55%
Kawashima 2005	Protons (30)	Phase II	2-yr LPFS: 96%	2-yr OS: 66%
Komatsu 2011 (Hyogo)	Protons (242)	Prospective study	5-yr LC: 90.2%	5-yr OS: 38%
Imada 2011[†]	**Carbon ions (226)**	**Phase I/II + II** **49.5 GyE/15 fr–52.8 GyE/4 fr**	**5-yr LC: 81–96%**	**5-yr OS: 25–35%**
Imada 2011[†]	**Carbon ions (116/226)**	**Phase II** **52.8 GyE/4 fr**	**5-yr LC: 95%**	**5-yr OS: 35%**

Indication: Hepatocellular carcinomas				
Author, year	Treatment (number	Type of study	Efficacy	
Komatsu 2011 (Hyogo)	**Carbon ions (101)**	**Prospective study** **52.8–76 GyE/4–20 fr**	5-yr LC: 93%	5-yr OS: 36.3%
Weighted mean difference in 5-year local control rates between carbon ions (95%) and TACE + 3D RT (<30%) = +65%, but proton and carbon ion therapy appear to be equivalent (except for very large tumours: C>P)				

LC: Local control; LRC: Locoregional control; DFS: Disease-free survival; OS: Overall survival; LPFS; Local progression-free survival; PFS: Progression-free survival; TACE: Transcatheter arterial chemoembolisation; 3DRT: three-dimensional conformal radiotherapy; N/A: Not available
†Update provided at the 2nd NIRS-ETOILE Joint Symposium 2011 in Lyon, France.

References:

Bush, et al. *«The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: A phase 2 prospective trail », Cancer 2011; 117:3053-3059.*
Imada et al. *"Carbon ion radiotherapy for liver cancer", Proceedings of NIRS-ETOILE 2nd Joint Symposium 2011 on carbon ion radiotherapy November 2011:46–53.*
Habermehl et al. *"Hypofractionated carbon ion therapy delivered with scanned ion beams for patients with hepatocellular carcinoma - feasibility and clinical response", Radiat oncol 2013 [epub ahead of print].*
Kato H et al. *"Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis", Int. J. Radiation Oncology Biol. Phys 2004; 59: 1468–1476.*
Kato H et al. *"Carbon ion radiotherapy for hepatocellular carcinoma"Proceedings of NIRS-ETOILE Joint symposium on carbon ion radiotherapy, March 2009: 57–63.*
Kawashima et al. *"Phase II study of radiotherapy employing proton beam for hepatocellular carcinoma", J Clin Oncol 2005; 23:1839–1846.*
Komatsu et al. *"Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma", Cancer 2011; 117:4890 -4904.*
Li et al. *"Study of local three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for patients with stage III hepatocellular carcinoma", Am J Clin Oncol. 2003;26:e92–e99.*
Yamada et al. *"Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma", Int. J. Radiation Oncology Biol. Phys. 2003:57;113–119.*

II.3 New Data on Prospective Indications

The most recent publications of the NIRS and HIT cover new indications that might be considered as prospective indications. The table below provides an overview of these results, updated in June 2013:

Table XX

Oesophagus

Author, Year	Study type	Location	Radiation dose	Evaluation criteria	Local Control	Follow-up duration	Result of evaluation criteria	No. of patients	Toxicity: early (ET), late (LT)
YASUNORI AKUTSU 2012	Phase I/II	Oesophageal squamous cell carcinoma (ESCC)	Initial carbon dose of 28.8 GyE up to 36.8	Overall survival	38.7% complete response	1 year (y1) 3 years (y2) 5 years (y3)	Stage I: 91% (y1)– 81% (y2)–61% (y3) Stage II: 100% (y1)–85% (y2)–77% (y3) Stage III: 71% (y1)–43% (y2)–29% (y3)	31	ET: 3,8% (1 case) respiratory distress syndrome LT: 0%

Meningiomas

Author, Year	Study type	Location	Radiation dose	Evaluation criteria	Local Control	Follow-up duration	Result of evaluation criteria	No. of patients	Toxicity: early (ET), late (LT)
STEPHANIE E COMBS 2013	Prospective observational study	Meningiomas - Benign (B) - High-grade (HG) - Recurrence (R)	(B): 52.2 – 57.6 GyE with protons (HG): boost with 18 GyE carbon ions + median dose of 50 GyE conformal radiation (R): - 19 patients: carbon 45–51 GyE in 3 GyE single fractions - 5 patients: proton (54 GyE or 57.6 GyE)	- Overall survival - Treatment planning (to define target volume)	100% for benign meningioma	2–22 months (median 6 months)	Overall survival - Low grade: 100% at 6 months - High-grade: (19%) of tumor recurrence during follow-up - Recurrence: 1 patient at 17 months (photon and carbon ion boost) To define target volume PET-imaging based on Ga-DOTATOC provides a better distinction between some areas of normal tissue and residual meningioma, especially after surgical resection.	70	Side effects/toxicity headaches (29%), nausea (24%), dizziness (23%), motor deficits (24%), sensory deficits (23%), seizures (1 patient), double vision (24%), oculomotor paresis (6%), trigeminal deficits (7%), abducens paresis (7%), postoperative facial lesion (1%), hypoglossal impairment (1%)

Astrocytomas

Author, Year	Study type	Location	Radiation dose	Evaluation criteria	Follow-up duration	Result of evaluation criteria	No. of patients	Toxicity: early (ET), late (LT)
AZUSA HASEGAWA 2011	Phase I/II	Astrocytomas	24 fractions over 6 weeks of carbon from 50.4 Gy equivalent (GyE) to 55.2 GyE	- Progression-free survival - Overall survival - Radiation dose	Mean of 62 months (10–152)	Progression Free Survival 18 months for low dose 91 months for high dose Overall survival 28 months for low dose Not reached for high dose Radiation dose Low dose: 46.2 GyE to 50.4 GyE High dose: 55.2 GyE	14	ET: Skin reactions: RTOG grade 2: 14% No RTOG grade 1 (14%) LT: - Skin reaction grade 1 (14%) - Brain reaction grade 3: (29%) for low-dose group and 40% in the high-dose group

Prostate

Author, Year	Study type	Location	Radiation dose	Evaluation criteria	Follow-up duration	Result of evaluation criteria	No. of patients	Toxicity: early (ET), late (LT)
TOHRU OKADA 2012	Retrospec-tive observa-tional study	Prostate	Carbon 20 fractions: 63 GyE or 66 GyE 16 fractions: 57.6 GyE	Biochemical relapse-free (BRF) Overall survival (OS) Hypofractionated treatment (16 vs 20)	5 years	- Biochemical relapse-free: 89.7% - Overall survival: 95.2% - Hypofractionated treatment: Advances in hypofractionation could be safely achieved with C-ion RT for prostate cancer.	740	LT: 16 fractions could offer an even lower incidence of genitourinary toxicity than 20 fractions, with comparable BRF rate.

Pancreas

Author, Year	Study type	Location	Radiation dose	Evaluation criteria	Local Control	Follow-up duration	Result of evaluation criteria	No. of patients	Toxicity: early (ET), late (LT)
MAKOTO SHINOTO 2013	Phase I	Resectable pancreatic cancer	Carbon from 30 Gray equivalents (GyE) to 36.8 GyE	- Survival rate - Safety of preoperative, short-course carbon therapy	0% local recurrence	5 years	Survival rate: 42% No serious adverse effects observed	26	ET: - Gastrointestinal: 1 patient with NCI-CTC grade 1 - Liver: 1 patient with NCI-CTC grade 3 LT: RTOG/EORTC grade 4 - Portal vein: 1 patient

Lung

Author, Year	Study type	Location	Radiation dose	Evaluation criteria	Local Control	Follow-up duration	Result of evaluation criteria	No. of patients	Toxicity: early (ET), late (LT)
NAOYOSHI YAMAMOTO 2012	Retro-spective study of clinical results	Oligo-recurrence in the lung	Carbon between 40 Gray equivalents (GyE) and 80 GyE, and fraction size ranging from 1 to 16 fractions	- Overall survival	In 116 lesions: 91.9%	Median 2.3 years (0.3–13.1)	Overall survival: 71.2%	91	ET: (NCI-CTC) - Skin reactions: 100% grade 1 - LT: (RTOG/EORTC) Skin reactions: 94.8% grade 1

References:

Akutsu Y, *Yasuda S, Nagata M, Izumi Y, Okazumi S, Shimada H, Nakatani Y, Tsujii H, Kamada T, Yamada S, Matsubara H. "A phase I/II clinical trial of preoperative short-course carbon-ion radiotherapy for patients with squamous cell carcinoma of the esophagus". J Surg Oncol. 2012 Jun 15; 105 (8):750–5.*

Combs SE, *Welzel T, Habermehl D, Rieken S, Dittmar JO, Kessel K, Jäkel O, Haberkorn U, Debus J. "Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and 68Ga-DOTATOC-PET". Acta Oncol. 2013 Apr; 52(3):514–20.*

Hasegawa A*, Mizoe JE, Tsujii H, Kamada T, Jingu K, Iwadate Y, Nakazato Y, Matsutani M, Takakura K. "Experience with carbon ion radiotherapy for WHO Grade 2 diffuse astrocytomas". Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):100–6.*

Okada T, *Tsuji H, Kamada T, Akakura K, Suzuki H, Shimazaki J, Tsujii H; Working Group for Genitourinary Tumors. "Carbon ion radiotherapy in advanced hypofractionated regimens for prostate cancer: from 20 to 16 fractions". Int J Radiat Oncol Biol Phys. 2012 Nov 15;84(4):968–72.*

Shinoto M*, Yamada S, Yasuda S, Imada H, Shioyama Y, Honda H, Kamada T, Tsujii H, Saisho H; Working Group for Pancreas Cancer. "Phase 1 trial of preoperative, short-course carbon-ion radiotherapy for patients with resectable pancreatic cancer". Cancer. 2013 Jan 1;119(1):45–51.*

Yamamoto N, *Nakajima M, Tsujii H, Kamada T. "Carbon ion radiotherapy for oligo-recurrence in the lung". Pulm Med. 2013; 2013:219746.*

II.4. Ongoing Clinical Trials

Clinical experience of hadron therapy was gained via successive feasibility and dose-escalation studies until the first dedicated European facility opened in Heidelberg. By analogy with drug trials, one might speak of **phase I and phase II** trials. These studies have made it possible to develop active, reliable, reproducible protocols. Basically they are retrospective or historical comparisons, and are summarised in the tables in the preceding chapter.
Since the Heidelberg facility became operational at the end of 2009, a series of prospective trials, including **randomised comparative trials, has been begun**. In addition, the French public funded clinical research programme for cancer is funding the beginning of collaboration with France's National Health Insurance Body and the Heidelberg and CNAO facilities, sponsored by the Hospices Civils de Lyon, to conduct an international randomised trial involving 250 French patients. On the basis of the comments in page 8 of the preamble, the expected difference in survival rate is between 20% and 25%, which should make it possible to draw conclusions from **relatively small cohorts, but certainly beyond 5 years**, for some slow-progressing diseases (adenoid cystic carcinomas, etc.).

Interestingly, as with carbon ion therapy, there have been almost no randomised trials of proton therapy. Although there are some 40 dedicated facilities worldwide and the number of patients treated runs into the tens of thousands, these trials are beginning only now, particularly in the USA. Carbon ion therapy might therefore be said to be beginning this essential validation earlier, but it must also be stressed that only multicentre trials will be sufficiently active to conduct studies in suitable time periods, which means there must be sufficient care offer available. In France and Europe, the national infrastructure ***France HADRON***, funded by the *Programme d'Investissements d'Avenir* (France's *Future Investment Programme*), must be active in clinical research in both proton and carbon ion therapy. This makes it unrealistic to try to work only with the care offer available abroad: this will gradually close down as recruitment within each country becomes more and more significant.

Table XXI: Ongoing randomised comparative trials of carbon ion therapy

Name of trial, sponsor	Diseases included	Treatments compared	No. of patients to be enrolled
Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study. **Study no.: NCT01182779** **HIT (Heidelberg)**	**Chordomas at the base of the skull:** - Karnofsky Performance Score ≥60% - Age >18 years and <80 years - Informed consent signed by the patient - Histological confirmation of chordoma with infiltration of the skull base	**Comparator treatment:** 72 GyE protons **Experimental treatment:** 63 GyE carbon ions	**344** patients over 5 years Starting late 2010
Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study. **Study no.: NCT01182753** **HIT (Heidelberg)**	**Chondrosarcomas at the base of the skull:** - Karnofsky Performance Score ≥60% - Age >18 years and <80 years - Informed consent signed by the patient - Histological confirmation of low-/intermediate-grade chondrosarcoma with infiltration of the skull base.	**Comparator treatment:** 50 to 56 Gy E plus a boost up to 70 Gy E ± 5% in conventional fractionated proton therapy **Experimental treatment:** Carbon ion therapy at 45 Gy E and a boost up to a total of 60 Gy E ± 5%	**154** patients over 7 years Starting late 2010
Randomised phase I/II study to evaluate carbon ion radiotherapy versus fractionated stereotactic radiotherapy in patients with recurrent or progressive gliomas: The CINDERELLA trial. **Study no.: NCT01166308** **HIT (Heidelberg)**	**Low-grade gliomas recurring after radiotherapy:** - Unifocal, supratentorial recurrent glioma (primary histologies including any WHO Grade II or III glioma or glioblastoma) - Prior course of standard photon radiotherapy - Contrast enhancement on T1-weighted MRI and/or amino-acid-PET-positive high-grade tumor areas - Indication of re-irradiation - Age ≥18 years - Karnofsky Performance Score ≥60 - Written informed consent	**Comparator treatment:** Fractionated stereotactic radiotherapy with photons. Total Dose 36 Gy, 18 fractions, 2 Gy single dose **Experimental treatment:** Carbon ion radiation therapy. The total dose applied will be the RD determined in the Phase I part of the study protocol.	**56 + 380** patients over 3–4 years Starting late 2010

Randomized phase II study evaluating a carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: The CLEOPATRA Trial. **Study no.: ISRCTN37428883, NCT01165671.** **HIT (Heidelberg)**	**Glioblastomas undergoing initial treatment:** - Histologically confirmed unifocal, supratentorial primary glioblastoma - Macroscopic tumor after biopsy or subtotal resection - Indication for combined radiochemotherapy with temozolomide - Prior photon irradiation of 48–52 Gy to the T2-hyperintense area, resection cavity, areas of contrast enhancement adding 2–3 cm safety margin in combination with standard temozolomide - Registration prior to photon RT or within photon RT allowing the beginning of particle therapy ≤4 days after completion of photon irradiation - Beginning of study treatment (proton or carbon ion RT) no later than 12 weeks after primary diagnosis - Age ≥18 years - Karnofsky Performance Score ≥60 - Written informed consent	**Standard chemotherapy** with TMZ plus **Comparator treatment:** Proton radiation therapy as a boost to the macroscopic tumor. Total Dose 10 GyE, 5 fractions, 2 GyE single dose **Experimental treatment:** Carbon ion radiation therapy as a boost to the macroscopic tumor. Total Dose 18 GyE, 6 fractions, 3 GyE single dose	**150** patients over 3 years Starting late 2010
First French prospective randomised study of the medical and financial potential of carbon ion therapy **HCL (Lyon)** **HIT (Heidelberg)** **CNAO (Italy)**	i) **Adenoid cystic carcinomas** (ACCs) of the head and neck ii) **Sarcomas** (soft-tissues, osteosarcomas and chordomas except chondrosarcomas and chordomas at the base of the skull)	**Comparator treatment:** Radiotherapy alone, photons and/or protons, using the latest techniques (IMRT, stereotactic, protons, etc.) **Experimental treatment:** Carbon ion therapy (CTh) *ACC:* combined photon therapy and CTh. CTh at 24 GyE in 8 fractions in GTV; conformal IMRT with photons at 50 Gy in CTV. *Sarcoma:* CTh alone at 60 GyE in 20 fractions over 4 weeks.	**250** patients over 4 years Starting late 2013

References:

Anna V Nikoghosyan et al. *"Randomised trial of proton vs. carbon ion radiation therapy in patients with chordoma of the skull base, clinical phase III study HIT-1-Study". BMC Cancer 2010, 10: 607. http://www.biomedcentral.com/1471-2407/10/607*

Anna V Nikoghosyan et al. *"Randomised trial of proton vs. carbon ion radiation therapy in patients with low and intermediate grade chondrosarcoma of the skull base, clinical phase III study". BMC Cancer 2010, 10:606. http://www.biomedcentral.com/1471-2407/10/606*

Stephanie E Combs et al. *"Randomised phase I/II study to evaluate carbon ion radiotherapy versus fractionated stereotactic radiotherapy in patients with recurrent or progressive gliomas: The CINDERELLA trial". BMC Cancer 2010, 10:533. http://www.biomedcentral.com/1471-2407/10/533*

Stephanie E Combs et al. *"Randomized phase II study evaluating a carbon ion boost applied after combined radiochemotherapy with temozolomide versus a proton boost after radiochemotherapy with temozolomide in patients with primary glioblastoma: The CLEOPATRA Trial". BMC Cancer 2010, 10:478. http://www.biomedcentral.com/1471-2407/10/478*

P Pommier et al. *"Première étude française prospective randomisée de l'intérêt médicale et économique de la radiothérapie par ions carbone". Abstract of SFRO Conference, Paris, 2011.*

II.5. Tolerance Data

In early 2010, the HAS wrote the following:

> *"Carbon ion therapy can induce late toxicity. This has been associated with the following indications in particular: chordomas and chrondrosarcomas at the base of the skull, sarcomas of the soft-tissues and axial skeleton, choroid melanomas and ocular tumours…."*

Today, with an additional distance of three years and full analysis of complications from the longest experience available (in Japan), it seems that this toxicity, possibly noticed initially because protocols were still being developed, is now under control. What emerges from this experience is that carbon ion toxicity is rather less significant than that of photon therapy at equal tumour volumes, particularly if one remembers that photon therapy requires adjuvant and concomitant chemotherapy in order to improve treatment performance.

Nevertheless, the toxicity profile of carbon ion therapy includes particular features:

II.5.1. Acute Toxicity

For acute reactions, the small number of entrance channels for a particular session of carbon ion therapy (as with proton therapy) provides more exposure to skin reactions than current photon therapy (high-energy, multiple entrance channels, arc therapy). This is not especially concerning, and although significant toxicity (cutaneous necrosis) was recorded at the beginning of use at the NIRS, these situations no longer arise.

In the studies described above, the rates of acute toxicity of grade 3 are low in comparison to the local benefit obtained, and in comparison to conventional treatments.

- In Schultz-Ertner's studies of 2003 and 2004, carbon ion radiotherapy for **ACCs** shows a grade 3 acute toxicity rate of 12.5% and 6.8% respectively.
- For **mucosal melanomas** in Japan, carbon ion radiotherapy shows a grade 3 acute skin toxicity rate of 1.7% and a grade 3 mucitis rate of 17.5%.
- In Schultz-Ertner's phase I/II trial, in the 44 patients with **chordomas** at the base of the skull no grade 3 acute toxicity was observed following carbon ion therapy. In updates of the results for 96 patients the grade 3 acute toxicity rate was 5.2%.
- Finally, in Japan irradiation of **sarcomas of the axial skeleton** leads to grade 3 skin toxicity (superficial tumours) in 10.5% of cases in one study, and grade 3 acute toxicity in 1.2% in another.
- Still in Japan, treatment was well tolerated for **pelvic and hepatic irradiation**, with no acute toxicity of grade 3 or above in approximately 357 treatments administered.

Thus these studies appear to indicate that carbon ion therapy for these tumour locations causes acute toxicity in 1.2% to 17.5% of cases. The highest rates of grade 3 acute toxicity were observed in the specific situations of irradiation of mucosal tumours or tumours close to the surface of the skin (superficial hepatocellular carcinomas or very peripheral lung cancers).

II.5.2. Late Toxicity

For late reactions, in addition to the risk of secondary tumours, which is dealt with separately, treatment of radioresistant tumours (which naturally require a high biological dose) entails exposure to late toxicity in healthy tissues that are in contact with or even *inside* the tumour. This is the case for peripheral neuropathies in the treatment of paraspinal tumours and some sarcomas, for example. Here too, we must use the accumulated experience of Japan's NIRS and then of Europe as much as possible in determining tolerance limits of these at-risk organs and adapting our standard dosage limits to carbon ion therapy. Enough time has now passed for us to be able to detect, treat and effectively adjust practice. This means there is no real time problem in assessing these risks, but rather an experience to enlarge and to share. Also, proton therapy still has some distance to cover in this area, as its

neurological toxicity has not yet been fully resolved (optic nerve, brainstem, spinal cord, peripheral nerve) (Jones B et al).

In the studies described above, grade 3 late toxicity rates, like acute toxicity rates, are particularly low. If we initially consider experience gained in Germany, the following picture emerges:

- In studies of irradiation of **ACCs** by Schultz-Ertner in 2003 and 2004, the use of carbon ions did not lead to any cases of grade 3 late toxicity.
- In Schultz-Ertner's phase I/II study, in the 44 patients with **chordomas** at the base of the skull no grade 3 late toxicity was observed after carbon ion irradiation. In the update of the results for 96 patients, again no grade 3 late toxicity was observed.

In Japan a greater variety of situations has been described. Late toxicity is summarised in **Table XXII** below, by tumour type. This includes all updated data as presented at the second NIRS-ETOILE Joint Symposium in November 2011 in Lyon, France.

Table XXII: Summary of late toxicity data from the NIRS (Japan), 1994–2011

Tumour location/type	Protocols	Doses and fractions	Late toxicity rate	Comments
Skull base Chordomas (n = 76)	Phase I/II 4-1997 to 2-2004 n=28 Phase II 2004 to 2-2011 n = 48	48 to 60.8 GyE / 16 fr 60.8 GyE/16 fr	3 cases of brain, grade 2	Median follow-up 46 months (range 3–158)
Head & neck tumors of various types (ACC, MM, SCC, ADC, etc.), excluding sarcomas (n = 404)	Phase II protocols 9301/9504/9602 From 6-1994; 4-1996 and 4-1997	57.6 GyE/16 fr (n = 265) 64.0 GyE/16 fr (n = 142)	8 cases of skin, grade 2 (2%) 14 cases of mucosal, grade 2 (4%)	Median follow-up >50 months
Soft tissue sarcomas of the head & neck (n = 39)	Phase I/II protocol 0006, from 4-2001 to 2-2008 n=41	70.4 GyE/16 fr	For n = 39; No reaction of grade 2 or above	Follow-up lasting more than 6 months
Malignant mucosal melanoma (n = 103)	Phase II protocol 0007; from 4-2001 to 2-2011 n= 103	57.6 GyE/16 fr + chemotherapy DAV	For n = 103; No reaction of grade 2 or above	Follow-up lasting more than 6 months
Lung cancers (n = 129)	Phase II protocols 9802 / 0001 From 4-2003 to 8-2010	36.0 to 46.0 GyE/1 fr	For n = 128, skin reactions: 126 G1; 1 G2; 1 G3 For n = 126, lung reactions: 116 G1; 3 G2; 0 G3/4	Median follow-up 51 months (range 2.5–70)
Bone and soft tissue sarcomas, including chordomas (n = 514)	Phase I/II 6-1996 to 2-2000 n = 57 Phase II 4-2000 to 2-2011 n = 500	52.8 to 73.6 GyE/16 fr 70.4 GyE/16 fr	For n = 506, skin reactions: 4 G0; 475 G1; 20 G2; 6 G3; 1 G4; 0 G5 For n = 439, gastrointestinal tract reactions: 437 G0; 2 G1; no G2/3/4/5 For n = 46, spinal cord reactions: 45 G0; 0 G1; 1 G2; no G3/4/5	Median follow-up ≈ 42 months (range 13–112)
Subgroup of sacral chordomas (n = 95*) *** Not included in total**	From 1996 to 2007	52.8 to 73.6 GyE/16 fr	For n = 95, 2 cases of G4 skin reaction requiring a skin graft; 15 cases of G3 sciatic nerve complications	Median follow-up ≈ 42 months (range 13–112). **After 2007, 88 more cases have been treated with**

Tumour location/type	Protocols	Doses and fractions	Late toxicity rate	Comments
				less toxicity (3 ports, 70.4 GyE/16 fr)
Liver cancer (n = 226)	Many protocols from 1995 to 2006; dose escalation and NBR of fraction reduction. Standard protocol: 52.8 GyE/4 fr	79.5 GyE/15 fr to 38.8 GyE/2 fr	For n = 226, no cases of grade 4 liver toxicity Child-Pugh score increased by ≥2 points in 5% and 7% in the small and large tumor group (≤ or > 5 cm) respectively.	Follow-up lasting more than 3 months
Recurrent rectal cancer after initial surgery alone (n = 140)	Phase I/II 4-2001 to 2-2004 n = 38 Phase II 4-2004 to 2-2010 n = 102	Dose escalation: 67.2 to 73.6 GyE/ 16 fr Standard: 73.6 GyE/16 fr	For n = 102, the only delayed effects were 4 cases of pelvic abscess after tumor necrosis (no relapse).	Follow-up lasting more than 3 months
Recurrent rectal cancer after initial surgery and radiotherapy (n = 23)	Phase II	70.4 GyE/16 fr	For n = 23, delayed effects were 6 cases (26%) of peripheral neuropathy and infection.	Follow-up lasting more than 3 months
Prostate cancer (n = 1305)	Phase I/II studies then phase II and standard	66.0 GyE/20 fr n = 250 63.0 GyE/20 fr n = 216 57.6 GyE/16 fr n = 539	Late tox ≥ grade 2: rectum and GU: 3.2 and 13.6% 2.3 and 6.1% 0.6 and 1.9%	Follow-up lasting more than 12 months
Total: n = 2959			**Late tox ≥grade 2:** **n' = 3523 exposed sites in treated patients** **n"= 140 observations of late toxicities** **4% (n"/n')**	

These results appear to indicate that with these tumour locations carbon ion therapy causes late toxicity of grade 2 or above in approximately 4% of cases. Only one patient of all those included in these studies presented grade 4 toxicity. This was a case of skin toxicity, which was successfully resolved using a skin graft.

Carbon ion therapy is clearly less toxic than photon therapy performed in comparable situations, specifically curative *in situ* tumour treatment (Thariat J et al; Revue 1, Revue 2). Equally clearly, it should not be compared to standard prophylactic radiotherapy, which must be absolutely non-toxic and currently accounts for nearly 40% of indications of radiotherapy (adjuvant treatment before or after surgery for rectal cancer, breast cancer, H&N cancer, lung cancer, sarcomas, etc.). With these indications radiotherapists cannot be certain that they are providing a benefit to the individual patient (knowledge in this area is purely statistical). Treatment must therefore be as little harmful as possible.

II.5.3. <u>The Risk of Secondary Cancer</u>

The risk of secondary cancer has been mentioned throughout the history of the development of hadron therapy. Some say the risk is substantial, which no objective information has supported after more than

10,000 patients have received carbon ion therapy and more than 100,000 have received proton therapy; others say insufficient time has passed even though the first proton and helium treatment was administered in the USA more than 50 years ago!

The most interesting experience in this area is that gleaned from the USA, as it brings together three advantages:

- Indisputably sufficient time (more than 50 years)
- The variety of particles used (including particles that are heavier than carbon – neon, argon, silicon – which are considered more carcinogenic than carbon in terms of radiation protection)
- Follow-up in a country with a good awareness of sanitary safety.

Two studies were conducted in patients treated between 1975 and 1986 at the LNBL, USA (personal communication from Blakely et al). This group of patients included two cohorts: 609 patients treated with helium and 299 treated with neon. Analysis concerns patients who had received a dose of 30 GyE or above and were followed up for 2 years or more.

For patients treated with helium (n = 609) 425 met the study criteria and 262 were treated for choroid melanomas. The mean follow-up time was 5.5 years. Three secondary tumours were observed in these 425 patients, a rate of 0.7%. The latency period ranged from 1.5 to 10 years, and the 3 tumours observed were 2 fibrosarcomas and 1 osteosarcoma, corresponding fairly typically to radiation-induced tumours.

Of the patients treated with neon (n = 299), 92 met the study criteria, with a mean follow-up time of 5.5 years. Two secondary tumours were observed in these 92 patients, a rate of 2.2%. Latency ranged from 6 to 6.5 years and the 2 tumours observed were 1 sarcoma with no further description and 1 angiosarcoma. The patient who developed the angiosarcoma was exceptionally susceptible to cancer: he had undergone photon radiotherapy for retinoblastoma and then received neon for an osteosarcoma, probably radiation-induced as a result of the first treatment, and developed an angiosarcoma 6 years after the second radiation therapy. These tumours are also fairly typical of radiation-induced tumours.

If we exclude this last patient, who does not really represent cancer specifically caused by hadron therapy, we obtain a risk of secondary cancer of approximately 1% in patients receiving helium (heavier than protons but lighter than carbon ions) and neon (heavier than carbon ions). In view of the populations examined, the 95% confidence interval for this risk is (95% CI 0.14%–1.86%).

We can therefore conclude from these data that the risk can be seen perfectly clearly with the time that has already elapsed since the series performed in the USA, Japan and Europe; it is between 0.1‰ and 2% of patients treated. Bearing in mind the indications on which hadron therapy is effective, this risk is negligible and compares very favourably with the risk of surgery or chemotherapy (NG Ak et al; Case Studies 39).

In addition to empirical information, theoretical studies have also been conducted to evaluate how the three characteristic parameters of hadron therapy may interact with each other with regard to the risk of cancer. These three parameters are as follows:

- The considerably smaller irradiated volume, which provides protection
- The production of diffuse neutrons, a risk factor
- The rather irreparable and therefore lethal nature of genomic lesions caused by heavy particles, which provides protection

Accordingly Uwe Schneider et al (PSI, Switzerland) (Schneider U et al; Miralbell R et al) performed a simulation of the cumulative risk of secondary cancer for remaining life expectancy (example: 37-year-old patient) following mantle-field radiotherapy for Hodgkin's disease, with radiation at a dose of 36 Gy. This situation typifies the risk of secondary cancers, which has been well demonstrated by epidemiology studies. At 15 years' follow-up, the population of patients cured of Hodgkin's disease has a relative risk of secondary cancer of between 20 and 100 in comparison to the general population; the figure varies between cohorts (Ng AK & Mauch PM). These authors show that the risk is lower with proton therapy than with conventional photon therapies: two-beam photon therapy 25.6%; multi-beam photon IMRT

25.8%; single-beam proton therapy 10.2%; multi-beam proton therapy 12.5%. From these results the authors develop a concept of "avoidable risk", which clearly favours hadrontherapy:

For heavier ions, such as carbon ions, the relative biological efficacy also comes into play. This implies both greater destructive power and greater mutagenic power for irradiated cells. These two factors tend to cancel each other out, and it can be shown that above a certain dose, easily attained by treatments such as those proposed (few entrance channels, high dose per fraction) destructive power outweighs mutagenic power, and there is no increased risk of secondary cancer (Jones B (2)). These studies explain why hadron therapy's supposed mutagenic power has not been observed, and why it should no longer be expected when there are already thousands of patient-years available for consultation.

References:

Jones B, *Wilson p, Nagano A, Fenwick J, McKenna G. Dilemmas concerning dose distribution and the influence of relative biological effect in proton beam therapy of medulloblastoma. BrJRadiol.2012 May2.*
Jones B (2) *Modelling carcinogenesis after radiotherapy using Poisson statistics: implications for IMRT, protons and ions. J Radiol Prot. 2009 Jun;29(2A):A143–57.*
Miralbell R, *Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. Int J Radiat Oncol Biol Phys. 2002 Nov 1;54(3):824–9.*
Ng AK, *Kenney LB, Gilbert ES, Travis LB. Secondary malignancies across the age spectrum. Semin Radiat Oncol. 2010 Jan;20(1):67–78.*
Ng AK, Mauch PM*. Late effects of Hodgkin's disease and its treatment. Cancer J. 2009 Mar–Apr;15(2):164–8.*
NIRS et al. *Proceedings of NIRS-ETOILE 2nd Joint Symposium 2011 on carbon ion radiotherapy November 2011: 12–72.*
Revue 1: *Screening for late effects. In Cancer Treat Res. 2009;150. (Complete monograph on side effects of radiotherapy in oncology)*
Revue 2: *Radiation dose-volume effects. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl).(Complete monograph on side effects of radiotherapy in oncology)*
Schneider U, *Lomax A, Lombriser N. Comparative risk assessment of secondary cancer incidence after treatment of Hodgkin's disease with photon and proton radiation. Radiat Res. 2000 Oct;154(4):382–8.*
Schulz-Ertner D et al. *"Results of carbon ion radiotherapy in 152 patients." Int J Radiat Oncol Biol Phys. 2004; 58(2):631–640.*
Schulz-Ertner D et al. *"Acute radiation-induced toxicity of heavy ion radiotherapy delivered with intensity modulated pencil beam scanning in patients with base of skull tumors." Radiother Oncol, 2002;64:189–195.*
Schulz-Ertner D et al. *"Effectiveness of carbon ion radiotherapy in the treatment of skull-base chordomas." Int. J. Radiation Oncology Biol. Phys. 2007;68(2):449–457.*
Série Études – 39, *Étude pilote pour l'estimation du risque iatrogène dans les établissements de santé en France, Final Report, Volumer 1 (pdf, 281.1 Kb, 01/11/2003, (MAJ:25/04/2012));* *http://www.drees.sante.gouv.fr/IMG/pdf/serieetud39a.pdf*
Thariat J, *Bolle S, Demizu Y, Marcy PY, Hu Y, Santini J, Bourhis J, Pommier P. New techniques in radiation therapy for head and neck cancer: IMRT, CyberKnife, protons, and carbon ions. Improved effectiveness and safety? Impact on survival? Anticancer Drugs. 2011 Aug;22(7):596–606.*

III. Data on the Health Economics of Carbon Ion Therapy

III. 1. Current data from the literature on the cost of carbon ion therapy

In general, publications on the health economics of hadrontherapy remain rare. A very brief analysis of the available literature is as follows:

a) Publications on health economics observations and data
Three publications provide observational retrospective cost study:

i) The publication by NP Ploquin et al compares the costs of conventional radiotherapy in various countries, mainly English-speaking, with comparable levels of health care. It yields comparable average costs per patient for all countries studied. They also propose a study of the development of these costs over time.

ii) The publication by Y Nakagawa et al studies the complete technical cost of hadrontherapy in Japan in three forms: protons, carbon ions and BNCT. It is based on infrastructure, operation and staff costs. The estimated costs are obviously incomplete, as they include neither the medical environment in which the disease is treated nor accommodation and travel costs. In addition, the number of patients treated per year varies between establishments. This means that a change from 500 to 1000 patients treated per year logically results in the price being reduced by approximately 50%. As ETOILE proposes treating approximately 1000 patients per year with carbon ion therapy in order to be financially viable, at this level of activity this part of the technical cost of carbon ion therapy in Japan is on average of $16,000. The "medical environment"of treatment accounts for a further approximately $14,000, as the NIRS's price is invoiced at $30,000 (figure for 2010).

iii) Finally, the publications by O Jäkel et al and A Mobaraki et al, analysed in detail below. They compare the medical efficacy of conventional treatments and carbon ion therapy for two of the leading indications of carbon ion therapy: chordomas at the base of the skull and pelvic recurrences of rectal cancers. These two studies are very cautious and tend not to exaggerate the differences between the two treatment approaches; the results nevertheless clearly favour carbon ion therapy.

b) Publications proposing a conceptual approach to cost analysis: the publication by M Pijls-Johannesma et al. presents a reflection based on costs and the actual costs of treatment, and proposes a simulation of patients' future according to treatment provided, described as a three-state Markov model. This method is used routinely in clinical trials to validate or follow up patients receiving hadrontherapy in order to reinforce still limited knowledge in this field.

c) Finally, two articles (Boston): one considering the lack of benefit of a medical demonstration going beyond physical evidence of the potential of proton therapy (H Suit et al), and one (A Zietman) drawing attention to the desirability of achieving consensus on the indications of proton therapy and to comply with this consensus on penalty of additional costs for public systems. These ideas might also be applied to carbon ion therapy.

References:

Baron MH, *Pommier P, Favrel V, Truc G, Balosso J, Rochat J. A "one-day survey": as a reliable estimation of the potential recruitment for proton- and carbon-ion therapy in France. Radiother Oncol. 2004 Dec;73 Suppl 2:S15–7.*

Jäkel O et al. *On the cost-effectiveness of carbon ion radiation therapy for skull base chordoma. Radiation and Oncology 2007; 83: 133–138.*

Mobaraki A, *T Ohno, S Yamada, H Sakurai, T Nakano. Cost-effectiveness of carbon ion radiation therapy for locally recurrent rectal cancer. Cancer Sci April 2010.*

Nakagawa Y et al. *Cost analysis of radiotherapy, carbon ion therapy, proton therapy and BNCT in Japan. Applied Radiation and Isotopes 2009; 67: S80–S83.*
Pijls-Johannesma M., *Pommier P., Lievens Y. Cost-effectiveness of particle therapy : current evidence and future needs. Radiotherapy and Oncology 2008 ; 89 : 127-134. Updated in:*
De Ruysscher D*, Mark Lodge M, Jones B, Brada M, Munro A, Jefferson T, Pijls-Johannesma M. Charged particles in radiotherapy: a 5-year update of a systematic review. Radiotherapy and Oncol. 2012;103:5-7*
Ploquina NP, *Dunscombea PB. The cost of radiation therapy. Radiotherapy and Oncology; 2008; 86: pp 217–223*
Suit H et al. *Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. Radiotherapy and Oncology 2008; 86: 148–153.*
Zietman A. *The Titanic and the iceberg: prostate proton therapy and health care economics. J of Clin Oncol 2007; 25: 3565–66.*

III. 2. Prices used or negotiated for proton and carbon ion therapy

In France, proton therapy has been reimbursed by Social Security for several years. Its CCAM code is ***ZZNL045***. The principle is exactly the same as for standard radiotherapy: a preliminary flat rate of €1,104 and a per-session rate of €1,017 (2012 prices). This means that, for example, "complete" proton therapy at 70 Gy using traditional fractionation over 35 sessions of 2 Gy per session will be invoiced to the health insurance provider at €36,699. This example shows just how burdensome proton therapy's multi-fractionated nature can be (the same is true of photontherapy).

This price is actually unusually "reasonable". Similar proton therapy in the USA frequently costs $150,000, approximately €111,000. These prices are based on a different financial logic from prices in Europe, because American facilities are for-profit institutions.

For carbon ion therapy, currently only the NIRS in Japan and HIT in Heidelberg provide carbon ion therapy for both national and foreign patients. CNAO, the Italian facility, opened in 2011 for proton therapy and began carbon ion therapy in the second half of 2012 will open for foreign patients, but European, during fall 2013.
Examination of each of these facilities individually provides an initial idea of what prices offered to patients are and might be. In general, flat rates are used, although there might perhaps be a more modular approach once these facilities are actually operational.

At the NIRS, the official price of carbon ion therapy is ¥3,140,000, equivalent to €32,000 (exchange rate as of May 2012). This cost is only for carbon ion therapy that was approved by the Japanese health authorities around six years ago. It corresponds to the current operating methods used in Japanese facilities and may change over time, most probably increasing if facilities are less supported by public funds and that new facilities will be built using borrowed money (Tosu-Saga, Kanagawa, ...). This price does not include associated costs such as inpatient admission and ongoing associated care, etc. In addition, this is the price used for patient insurance, but is not an opposable reimbursable price for any universal insurance system such as the French CNAM, with the ALD (Long Duration Diseases) system.

In Germany:
The flat rate for a full course of carbon ion therapy negotiated with health insurance companies (Jäkel O et al) was fixed at €19,500 in 2007, excluding additional medical costs probably assumed by mutual or insurance companies. This price has recently been revised to distinguish short treatment of less than 10 sessions, the fare is €13,000, and the regular full treatments of 10 or more sessions billed €25,350. The Heidelberg facility, of which half of the construction costs were funded by public subsidy, is currently the only operational facility in Germany. The facilities at Marburg and Kiel, both built by Siemens, have experienced contractual difficulties that have led Siemens to withdraw from particle therapy. According

to the most recent information available, the Kiel facility has been uninstalled and the Marburg facility is waiting for a decision for it future opening sine die.

The situation in Germany has therefore changed a great deal over the last few years. The situation in Japan, meanwhile, is much healthier and is maturing, with four competing industrial entities able to build such facilities.

Finally, in Italy, the CNAO facility opened in September 2011. Its construction was 100% financed by subsidies, 86% from the public sector, and no money was borrowed. This means there is no financial investment burden on treatment costs. The principle of a flat rate with three levels according to the complexity and number of treatment sessions was agreed upon in 2007–2008, and discussions on pricing concluded with the results shown in Table XXIII (R Orrechia, personal communication, 31 August 2009, confirmed July 2013) below.

Table XXIII: Italian rates negotiated in 2009, before the opening of CNAO in 2012

Price of hadrontherapy for CNAO, Italy, negotiated in 2009			
Type of beam	Stereotactic treatment, 1–3 fractions	Boost, up to 6 fractions	Full treatment, 12–16 fractions
Protons	€16,000–€17,000	€10,000–€11,500	€24,000
Carbon ions	€19,000	€12,000–€14,000	€24,000

As these prices predate the opening of CNAO to reimbursed treatments, they may be revised after it opens.

To date there is no known information on forecast prices in the USA, but in view of the very profitable American proton therapy prices, much higher costs can be expected than in Europe or Japan.

For subsidised facilities (which have no financial burden other than operating and maintenance costs), there is thus a kind of European-Japanese cost convergence at around €28,000 for carbon ion therapy. **A price of approximately €35,000 (figure for 2012) for carbon ion therapy seems a reasonable estimate for France when its facility opens, as the ETOILE Centre will be essentially financed by borrowing.**

Finally, the table below provides an estimate of the additional cost of treatment of a French patient abroad for the main carbon ion therapy facilities. In general, the additional cost of treatment abroad would be approximately **€6,000 per patient**; see Table XXIV below.

Table XXIV: Additional costs for treatment abroad

Facilities providing carbon ion therapy	**NIRS**		**CNAO**		**HIT**		**MEDAUSTRON**	
Country	Japan		Italy		Germany		Austria	
City in which carbon ion therapy facility is located	Chiba		Pavia		Heidelberg		Wiener Neustadt	
Useful airports	Paris/Tokyo		Paris/Milan		Paris/Frankfurt		Paris/Vienna	
Item/price	**Unit price**	**Cost/ patient**	**Unit price**	**Cost/ patient**	**Item/ price**	**Unit price**	**Cost/ patient**	**Unit price**
LOGISTICS								
Travel								
Journey from home to Paris airport	120	120	120	120	120	120	120	120
Return aeroplane ticket	1,000	1,000	1,068	1,068	1,037	1,037	1,100	1,100
Return transfer from airport to hotel	20	20	30	30				

Facilities providing carbon ion therapy	**NIRS**		**CNAO**		**HIT**		**MEDAUSTRON**	
Return train journey from airport to facility	0	0	0	0	74	74	43	43
Accommodation								
Night at hotel*	70	2,170	80	2,480	80	2,480	80	2,480
Companions								
Day-to-day assistance, interpreter (part-time)	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Other costs								
Flat rate for meals (3/day)	20	620	20	620	20	620	20	620
Flat rate for local travel (2/day x17)	15	510	15	510	15	510	15	510
Total logistics		**5,440**		**5,828**		**5,841**		**5,873**

CARE								
Carbon ion therapy		32,000		24,000		24,000		?
Medical care not covered by flat rate for therapy		1,500		1,500		8,500		0
Total care		**33,500**		**25,500**		**32,500**		**?**

TOTAL		**38,940**		**31,328**		**38,341**		**?**

Costs in Euros, taxes included (except local tourist taxes)

Basic conditions for evaluation of prices for all countries:

*Single-room accommodation, no lunch or dinner.

Length of stay: 31 nights. 2-stars hotels. *N.B.: Prices are provided for information only and are not guaranteed.*

Country-specific conditions:

Japan: Medical care not covered by flat rate for therapy. One preparatory week (4 sessions) followed by three weeks of carbon ion therapy (12 sessions plus 1 visit before departure).

Italy: Flat rate with three tiers according to the complexity and number of treatment sessions.

It must be stressed that to date no foreign dedicated facility has routinely included large numbers of foreign patients in its activity. It can easily be seen that Germany and Italy remain underequipped in relation to their national populations. In particular, Heidelberg will reach its nominal full activity as soon as 2014. Therefore, when recruitment in these countries will be established, the access for foreign patients, and specifically French patients, will become very limited or even impossible.

III. 3. Report on Medical Benefit and Cost-Effectiveness

Carbon ion therapy, and even protontherapy, represent a real move away from the prices of conventional radiotherapy, even 3D intensity-modulated radiotherapy using one of the available techniques (there are several versions currently available, depending on the size, shape and anatomical location of the volume to be treated: Linac, Tomotherapy, Cyberknife, etc.). Conventional radiotherapy is by far the most efficient cancer treatment, both medically or financially (see chapter III.3 for comparative figures). It is unsurprising that hadrontherapy's high-tech nature and complexity of treatment stands out when compared to this standard base.

However, **the difference between cost per additional cured patient for conventional radiotherapy and hadrontherapy is not as large as it might at first seem.** It is actually quite easy to demonstrate that, for specific indications only, hadrontherapy may be more cost-effective than conventional treatments.[12]

First of all, in general the two techniques do not target the same patients. In particular, a very large proportion of conventional radiotherapy is either palliative care (more than 20%) or treatment that is adjuvant, prophylactic or combined with surgery (nearly 40%). **The health impact of this in terms of**

[12] O Jäkel et al, A Mobaraki et al.

curative ability is becoming lower and lower as a result of the combined progress of early diagnosis, surgery and adjuvant chemotherapy. Two examples demonstrate this: pre-operative radiotherapy for rectal cancer and post-operative radiotherapy for breast cancer.

For rectal cancer, routine pre-operative chemoradiotherapy for T3 or N+ tumours allows a threefold reduction in the risk of local recurrence.[13] This risk after surgery performed as recommended is currently between 7% and 15%. Radiotherapy (which is in fact chemoradiotherapy) will therefore reduce this risk to between 2% and 5%, and is therefore only really useful in 5% to 10% of patients treated. The reason all patients are treated is that we are not currently able to predict who really needs it. The result, however, is that 90% to 95% of patients are treated useless at the point of view of their individual benefit. The cost of one additional recovery as a result of radiotherapy is therefore 10 to 20 times that of the cost of the radiotherapy itself, i.e. well over €30,000 on average; it can be estimated that every year in France between 400 and 800 patients actually benefit from this treatment at this resultant cost. The question of continuing to perform such irradiation will certainly be raised, and is a very topical issue.[14]

For breast cancer the situation is less alarming: radiotherapy is part of breast-preserving treatment and reinforces surgery performed on tumours that are becoming smaller and smaller as result of better detection. Its impact is greater than for rectal cancer. It probably benefits 20% to 30% of patients. This means it triples or quadruples the price of one curative treatment, i.e. approximately €14,000–€18,500. In view of the frequency of this disease, this represents approximately 7,500 patients in France per year who actually benefit from this treatment at this resultant cost. Here too, current knowledge does not allow us to distinguish these patients either initially or retrospectively, but in response to this there is a development of exploratory practices: partial irradiation of the breast and peri-operative irradiation in a single session, etc.

Following this same logic, *on a purely speculative basis*, for all conventional non-palliative radiotherapy (see Table XXIV below), bearing in mind that palliative treatment and *in situ* tumour treatment are beneficial in 100% of cases, we come to the conclusion that only around 20% (cumulative benefit adjustment coefficient, 4.9) of radiotherapy currently performed benefits the patients who receive it. Conventional radiotherapy is therefore five times more expensive than it seems at first glance in cases in which it is effective or at least directed at a present, threatening target, if compared to a treatment proposed only for patients with otherwise untreatable tumours like carbon ion therapy. This means its average cost is closer to €20,000 than to €3,000 or €4,000. Thus in terms of equal medical benefit hadron therapy is barely 1.5 times more expensive, and moreover for a very limited number of specific tumours that are otherwise difficult or even impossible to treat. Finally, in such cases hadron therapy replaces conventional radiotherapy and even much more expensive treatments such as targeted therapies.

These comments apply equally to adjuvant chemotherapy (breast, colon, lung and pancreatic cancers). This makes their benefit costs between 3 and 5 times above their apparent levels. This is also true of lung and pancreatic cancers, in which the clinical impact (medical benefit), while statistically significant, is actually very small.

[13] J Balosso et al. Traitements préopératoires (*Pre-Operative Treatments*). In: Monographie sur le Cancer du Rectum, French Surgeons' Association 2009, ed. E Rullier and JL Faucheron.

[14] Researchers and physicians at large institutions on the front line in the fight against cancer met on Thursday 9 and Friday 10 July 2009 in Paris as part of an initiative of the Institut Gustave Roussy (IGR) in Villejuif (Val de Marne) and the MD Anderson Cancer Center of the University of Texas in Houston, to consider personalised cancer treatments. This is the purpose of this event of WIN (Worldwide Innovative Networking in personalized cancer medicine).

Table XXV: Estimate of effective percentage of conventional radiotherapy

Location and indication of conventional radiotherapy	Relative percentage (%) A	Percentage of treatments that are useful (curative with impact on survival) (%) B	Benefit adjustment coefficient * C = 100/B	Contribution to overall benefit adjustment coefficient D = C × A/100
Palliative radiotherapy	Excluded from this model as its specific cost is often very low, because it is usually simplified and hypofractionated.			
ENT without surgery	10	100	1	0.1
Post-op ENT	10	65	1.53	0.153
Post-op breast	20	15	6.67	1.334
Prostate	20	30	3.33	0.666
Lung	15	20	5	0.75
Pre-op rectal	10	7	14.28	1.428
Brain tumours	7	100	1	0.07
Pancreas	6	20	5	0.3
Lymphomas	2	20	5	0.1
	100	--	--	4.901*
*In practice, this figure represents the number of patients who need to be treated in order to provide certain medical benefit to one patient.				

In addition to this essentially mathematical approach to cost comparison, a more health economics-based approach consists of **comparing the total costs of treatment, including recurrences and supportive treatments, for different approaches**. This has already been done for two specific indications of carbon ion therapy: chordomas (in Germany) and recurrences of rectal cancer (in Japan).

For chordomas of the base of the skull, O Jäkel et al (op cit[12]) show very convincingly that the total cost of treatment is lower for hadrontherapy (96 patients treated) than for conventional treatment, partly because it replaces other treatments and partly because it reduces the recurrence rate – and therefore the costs associated with the treatment of recurrences (without achieving cure) (10 recurrences selected at random and studied in detail) (see Table XXVI below).

Table XXVI: Comparative analysis of the total cost of treatment of chordomas using photons versus carbon ion therapy

5-year local control rate	Cost of primary treatment	Cost of recurrences	Total cost (€)	
			Long treatment	Hypofractionated treatment
35% (photons)	€27,100	**€52,956**	€80,056	--
50% (photons)	€27,100	**€40,735**	€67,835	--
60% (carbon)	€43,600	**€32,588**	€76,188	**€72,188**
70% (carbon)	**€43,600**	**€24,441**	€68,041	**€64,041**

For pelvic recurrences of rectal cancers, A Mobaraki et al (op cit[12]) analyse in much greater detail the cost-effectiveness of carbon ion therapy versus *conventional* treatments. The study is actually based on

a paired case series treated in a much more sophisticated manner than usually the case for conventional treatments (more complex, longer treatment that reduces the difference between it and carbon ion therapy, specifically using hyperthermia, which is rarely used worldwide). Comparison includes all direct costs of treatments, complications and repeat recurrences. It does not include indirect costs (productivity losses, suffering of loved ones, etc.). Comparison is also performed for the average of published series. The results are given both as absolute values and as ICERs (incremental cost-effective ratios). Using the yen exchange rate as it was when the study was conducted, ¥143.87 yen to €1.00, this means that carbon ion therapy allows better survival for patients treated than conventional treatments, at a price of €93.50 (ninety-three euros, fifty cents!) per additional year of recurrence-free survival, and €92 per percentage-point survival rate increase. In other words, in this study the increase in therapeutic benefit provided by carbon ion therapy completely cancels the additional cost involved.[15]

This approach is testable for all hadrontherapy indications and comprises a very strong argument in favour of these highly-targeted treatments, which (like all treatments) require absolute compliance with indications in order to perform well.

III. 4. Financial Comparison

The previous chapter compared the price of hadrontherapy to that of conventional radiotherapy. It is also useful to consider radiotherapy's place in health care costs and cancer treatment costs, and to include hadrontherapy in this process.

Health Care and Cancer Care Costs in France:[16]

Of a total of €167 billion spent on health care in France in 2011,[17] 8.6% of GDP, the **proportion spent on cancer care is between 8% and 11%, or approximately €15 billion**, for health insurance.

This expenditure provide for treatment of approximately 365,500 new patients per year.[18] Half of these patients will recover essentially as a result of effective surgery and radiotherapy for locoregional forms of these diseases. These two areas are also the most efficient in health economics terms. They cost the health care system €2.7 billion and €0.93 billion respectively, representing 18% and 6% respectively of cancer treatment expenditure (see table below).

Expenditure on radiotherapy in France:[16]

A closer look at **radiotherapy**, which is performed at approximately 180 health facilities in France, shows that it affects approximately 180,000 patients per year, with a mean total cost estimated at €5,200 per patient (an updated calculation based on figures from the table above). This figure seems comparable to those given in the literature. In fact, a comparative study of the cost of radiotherapy in six developed countries (the UK, Canada, the USA, Australia, Belgium and Sweden, but not France) published in 2008 (Ploquina NP et al) establishes an average of €3,240 for 2005 for one 21-session treatment (less than the French average of approximately 25.5 sessions). With a 3.6% annual increase[19], the 2011 value can be

[15] "The ICER for CIRT based on the calculated survival rate was ¥6428 per 1% increase in survival (€44.70€)…/…The average ICER for CIRT in terms of disease-free survival was ¥13 454/year (€93.50) of disease-free survival, while the average ICER due to CIRT per 1% increase in survival rate was ¥13 221(€92)."

[16] In 2007 the INCa published a report on the financial figures for cancer in France for 2004 (*Analyse économique des coûts du cancer en France* (*Financial analysis of the costs of cancer in France*), INCa, March 2007, 142 pp; http://www.e-cancer.fr/v1/fichiers/public/etude_economieducancer.p). These figures are therefore eight years old and have not been updated, or the updated version is not available. However the INCa report "Situation de la chimiothérapie en France en 2010" (*The status of chemotherapy in France in 2010*) and the opinion of the Academy of Medicine "Mise au point sur la prescription des molécules onéreuses en cancérologie"(*Update on the prescription of expensive in cancer care*, uploaded on 16 March 2011) does provide an idea of changes in the costs of medical treatments for cancer. In any case, we believe it is important to highlight the financial developments that have occurred in particular since the 28% increase in ONDAM (France's national target for health-insurance expenditure) and the 10% increase in the cancer cases over the same period. It therefore seems realistic to consider cancer accounting for a proportion of between 8% and 11% of expenditure in 2011, compared to 7–10% in 2004.

[17] Source: Eco-santé France 2012, IRDES and INSEE for GDP.

[18] InVS, figure for 2011, additional information on the incidence of cancers in France: http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/default.htm (in French).

[19] The average annual increase in ONDAM between 2005 and 2011.

estimated at €4,500–€5,000, comparable to the updated French figure. However, this comparison must be treated with caution.

Table XXVII: Costs for 2004, (reference : *Analyse économique des coûts du cancer en France* [*Financial analysis of the costs of cancer in France*], INCa, March 2007, p. 127)

ESTIMATE OF COSTS BY LOCATION AND TREATMENT TYPE

Anatomical location of tumour	Total (€)	Surgery		Chemotherapy		Radiotherapy		Other	
		€	%	€	%	€	%	€	%
Digestive tract	1 534 359 252	601 334 469	39%	358 487 013	23%	56 807 521	4%	517 730 249	34%
Blood	965 937 257	62 056 787	6%	263 020 654	27%	19 056 597	2%	621 803 219	64%
Breast	788 912 074	246 481 645	31%	208 803 268	26%	213 740 563	27%	119 886 599	15%
Respiratory tract	706 697 556	117 316 876	17%	203 511 262	29%	49 852 421	7%	336 006 998	48%
Male genital organs	506 566 276	214 965 069	42%	35 965 760	7%	122 438 652	24%	133 196 795	26%
Upper respiratory and digestive tracts	416 624 689	130 081 990	31%	57 577 067	14%	93 816 742	23%	135 148 889	32%
Urinary tract	394 514 883	233 611 450	59%	43 055 266	11%	8 285 180	2%	109 562 987	28%
Female genital organs	292 324 202	117 233 500	40%	71 330 056	24%	32 737 206	11%	71 023 439	24%
Skin	144 231 728	96 192 690	67%	10 330 057	7%	9 035 303	6%	28 673 677	20%
CNS	141 349 021	51 799 982	37%	12 347 850	9%	23 724 317	17%	53 476 872	38%
Thyroid and other endocrine glands	58 737 301	25 035 638	43%	2 230 152	4%	6 114 521	10%	25 356 990	43%
Soft tissues	45 004 533	10 621 759	24%	12 728 819	28%	6 855 378	15%	14 798 577	33%
Bone	44 798 445	12 747 633	28%	15 617 114	35%	2 970 767	7%	13 462 932	30%
Eye	7 322 193	3 270 298	45%	780 349	11%	909 058	12%	2 362 488	32%
Metastasis, SMD and other locations	1 062 506 113	210 907 504	20%	371 704 749	35%	92 162 142	9%	387 731 718	36%
Total	7 109 885 521	2 133 657 289	30%	1 667 489 436	23%	738 516 368	10%	2 570 222 428	36%

France's current hadrontherapy capacity is only 600 treatments per year for deep protontherapy and a few units per year for carbon ion therapy treated abroad, in Germany and Japan. If we estimate France's potential for carbon ion therapy for the next 10 or 15 years at 1,500–2,000 patients per year, which corresponds to priority indications[20] (Baron MH et al), a switch from conventional radiotherapy to hadrontherapy will thus be very gradual and limited, excluding any financial upheaval in the field. In 5–10 years from now, for all hadrontherapies (approximately 1,500 carbon ion treatments and 2,000 proton treatments), a maximum additional cost of approximately €89,000 can be envisaged for, probably, 850 additional recoveries (25%). This would represent 0.6% of oncology expenditure for 0.96% of patients, all "difficult" cases – rather a favourable figure.

Comparisons between cancer treatments (Figure 16):

It is difficult to compare anti-cancer treatments to each other, as they act in different ways and have very different aims. Regarding a curative approach to cancer, it must be acknowledged that only surgery and radiotherapy are really comparable, and we have already seen how much more cost-efficient they were than medical treatments for cancer.

Because carbon ion therapy is intended specifically for tumours for which surgery cannot provide a solution, it might be compared to the treatments used when surgery cannot be performed or when surgery fails due to the extent of the initial disease or metastatic recurrence.

Carbon ion therapy might also be compared to medical treatments for cancer that are intended for tumours that are too advanced for surgery: traditional anti-mitotic chemotherapy or chemotherapy based on targeted therapies such as those currently being developed. However, it should be noted that with the exception of adjuvant therapy, which can genuinely increase recovery rates (e.g. breast cancers that overexpress the oncogene C-erB2 and are treated with trastuzumab [Herceptin®] for one year), sadly all these targeted therapies have only a temporary effect in delaying tumour progression. As a result, they have to be combined or replaced with other similar treatments as the disease repeatedly recurs until the patient's death. Treatment is therefore very long; it is becoming more and more common for them to last for several years. They are also non-curative and are used in a steadily-growing number of patients and which require associated treatments that are themselves costly (anti-nausea

[20] Figures estimated on the basis of the one-day survey of the ETOILE project in 2003, ref: Baron MH et al. Almost identical figures are provided by Italian epidemiological studies of CNAO (R Orrechia, personal communication).

treatments, haematopoietic growth factors, implantable venous chambers, treatment for complications, etc.).

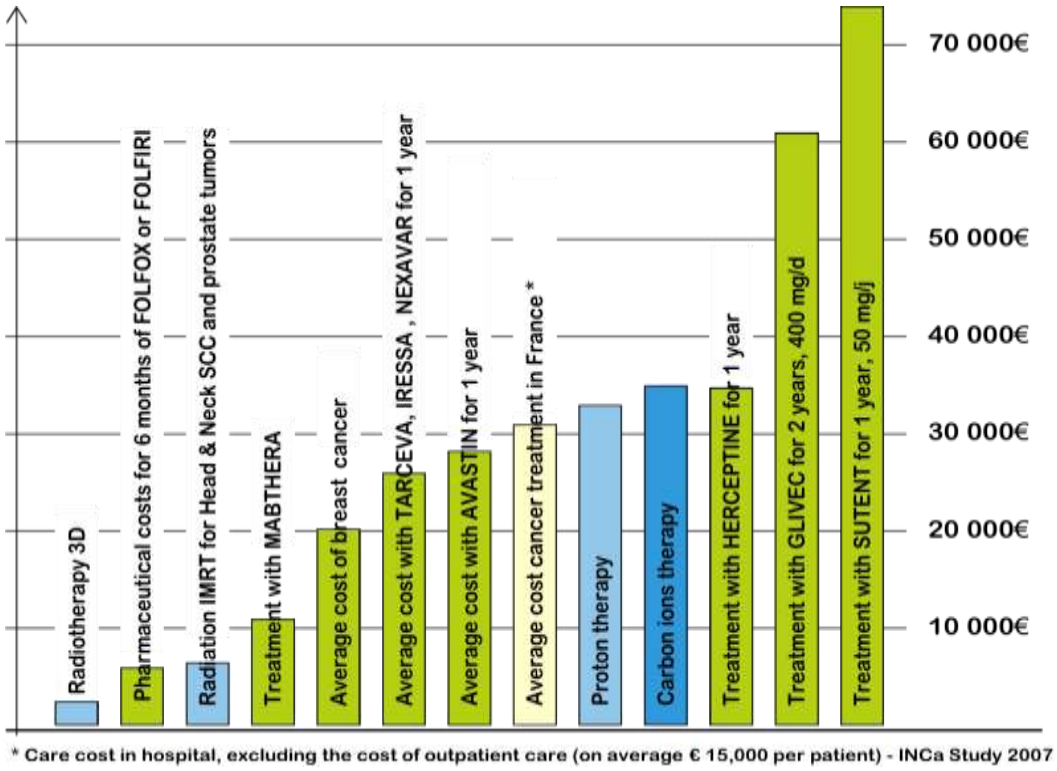


Figure 16: Histogram comparing the hospital cost of anti-cancer treatments in France, updated for 2011–2012[21]

As half of cancer patients die as a result, it can be estimated that in terms of incidences the potential for treatment in France is almost 150,000 new patients per year for medical treatments for progressive cancers. This potential increase is real, and has been recognised: ***"There is fast, sustained growth in the number of patients receiving chemotherapy in medical establishments in all sectors of private and public hospitalisation. More than 270,000 patients received these treatments in 2009. The number of patients treated increased by 9% between 2008 and 2009, and 24% over the last five years. The number of patients receiving chemotherapy is therefore growing faster than the number of new patients (twice as fast): this means that chemotherapy is being indicated for a growing proportion of cancer patients. [SITUATION DE LA CHIMIOTHERAPIE des cancers en 2010, INCa]."***[22] A duration of between 6 months to 2 years has been proposed for the comparison put forward in the figure above for this type of treatment. For the present, this is a realistic average, but it certainly does not entail equivalence: recovery achieved through hadron therapy provides more life expectancy than 2 years of medical treatment. An indexed approach to the cost per year of life expectancy (QALY)[23] would be extremely favourable to carbon ion therapy over medical treatments for cancer.

Three more differences should be highlighted between these medical anti-cancer treatments, which are novel and very expensive, and carbon ion therapy:

– **Carbon ion therapy will be performed as a curative treatment** and almost always provides a benefit to individuals in a very targeted population (unlike prophylactic and adjuvant treatments, which reduce the probability of a recurrence, often already small after surgery).

[21] Up-to-date information on drug indications, dosing and prices can be consulted at http://sante-az.aufeminin.com/w/sante/medicaments.html or http://www.atih.sante.fr/index.php?id=0001000029FF (in French).
This information can be summarised as follows: Herceptin, 1 year = €34,713; Avastin, 1 year = €28,437; Erbitux, 6 months = €21,814; Vectibix, 6 months = €22,125,60; Glivec 400 mg, 2 years = €61,063; Sutent, 1 year = €73,981; Nexavar, 1 year = €24,398; Iressa, 2 years = €55,297,50; Tarceva, 2 years = €52,428,60; Mabthera, 6 cycles = €11,013.

[22] The INCa report can be downloaded at "Situation de la chimiothérapie en France en 2010" (in French).

[23] QALY: *quality-adjusted life year*.

– **Carbon ion therapy will be very short and low in toxicity:** between 4 and 6 weeks, thus avoiding major additional costs associated with the duration of treatment, travel ("ambulance therapy") and associated supportive treatment (anti-nausea, haematopoietic growth factors, implantable venous chambers, treatment for complications, etc.) that are not included in these cost comparisons.
– **Carbon ion therapy will be targeted at a particular group of tumours**, of which there are considerably fewer than of cancers receiving medical treatment: a few thousand patients per year at the most (1,500–2,000 for the current population, and after approximately 5–10 years of progression).

IV. Future Perspectives

What still remains to be shown?

Studies of carbon ion therapy to date have primarily been phase I/II prospective case series and phase II studies with historical controls. Although in principle the choice of patients receiving carbon ion therapy has not been very favourable to the procedure (large tumours, repeated irradiation of recurrences, etc.), ***the superiority and cost-effectiveness of carbon ion therapy when compared to conventional treatments essentially concerns the indications that we have described as consolidated.***

Isolated studies of ***medical benefit*** in chordomas and recurrences of rectal cancers are convincing and reassuring, but are nevertheless retrospective comparisons obtained in a different health care context from that of France. ***Conduct of such studies is therefore to be encouraged***, particularly in the form of sub-studies of any prospective studies, for example (e.g. the ETOILE-ULICE public funded clinical research programme).

Paradoxically, until the ETOILE Centre opens, French patients can access carbon ion therapy at foreign dedicated facilities, but only in a very limited number. From this point onwards, the ethical question faced by radiotherapists in phase III clinical trials for consolidated indications no longer exists. This is why the ETOILE-ULICE public funded clinical research programme is being conducted as a randomized trial: to confirm treatment efficacy, evaluate its relative cost and, especially, provide initial experience for French radiotherapists and their patients.

As a result, there is currently a favourable time window in which both the development of a minimum number of benchmark facilities and the conduct of prospective, comparative trials must be encouraged simultaneously, for both medical and financial reasons. This is one of the aims of ***France HADRON***, and the ETOILE Centre in particular.

A medical evaluation procedure for prospective and exceptional indications will be conducted once there is a sufficient number of hadrontherapy facilities in Europe.

What remains to be improved?

The European FP7 and the French Future Investment Plan have made carbon ion therapy one of the ***future technologies to be promoted***. The procedure has matured to a stage suitable for medical use. The French project is emerging at a time when there is little European or American industrial competition, giving France an opportunity to develop this scientific and industrial niche. In fact, there are still many things that remain to be improved and optimised. To list them would be to list the aims of the large technical and scientific consortiums that have been established for this purpose in recent years.

One example is the French entity ***France HADRON***, which has divided its aims into the following four working areas:

WP1 : Clinical research for hadron therapy

- WP1.1 National hadron therapy collaborative group
- WP1.2 Data exchange platform and prospective databases dedicated to hadron therapy
- WP1.3 Clinical trial projects

WP2 : Improving treatment planning in hadron therapy

- WP2.1 Measurements of cross-sections and biological data
- WP2.2 et 2.3 Simulation tool and simulation platform for dose deposit and treatment
- WP2.4 Multimodal functional and metabolic imaging...

WP3 : Radiobiology for Hadron therapy

- WP 3.1 Methods for radiobiological data acquisition, processing, analysis, modelling
- WP 3.2.1 Radiobiological approach of combined or sequential hadrontherapy
- WP 3.2.2 Influence of hadron therapy on recurrence, angiogenesis and metastasis
- WP 3.2.3 Prediction of tumour response
- WP 3.3.1 Individual susceptibility and DNA damage repair and signalling
- WP 3.3.2 Toxicity of hadrons on healthy tissues
- WP 3.3.3 Risk of hadron-induced cancer

WP4 : Research and Development in instrumentation for treatment quality

- WP4.1.1: Imaging of beta+ emitters
- WP4.1.2: Prompt gamma Imaging
- WP4.1.3: Secondary proton vertex imaging
- WP4.2: Proton radiography
- WP4.3.1: Beam diagnostics and monitoring
- WP4.3.2 Neutron contamination
- WP4.4: Damage on electronics and microdosimetry

V. Conclusion

What is currently known about the medical potential of carbon ion therapy?

Since carbon ion therapy was first used in Japan in 1994, and then in Europe in 1998, absolutely unambiguous proof has been provided of its therapeutic efficacy and excellent tolerability. More than 10,000 patients have been treated to date, at six different facilities. ***There is no need of additional studies to confirm that for priority indications, indications known as consolidated, carbon ion therapy is an active, reliable, well tolerated anti-tumour treatment.*** Nevertheless, demonstrating its therapeutic and financial superiority to other techniques is a separate issue, one that must be addressed in different ways for priority and prospective indications.

For priority indications, essentially rare tumours, the demonstrated differences in outcomes mean they must be considered validated. On principle, they cannot give rise to systematic randomised comparative trials. With our current knowledge of these differences in outcome, this would be unethical and therefore unfeasible.

The eligible, priority indications of carbon ion therapy are currently as follows:

- **Tumours of the salivary glands**
- **Tumours of the paranasal sinuses**
- **Adenoid cystic carcinomas**
- **Mucosal melanomas**
- **Chordomas at the base of the skull**
- **Unresectable or incompletely resected sarcomas and chrondrosarcomas**
- **Local, unresectable recurrences of rectal cancers**
- **Single large hepatocellular carcinomas**

In France, these priority indications represent sufficient activity for a single facility to be financially viable; there they could be treated at a similar cost to protontherapy and enable the development of new prospective indications, with European collaboration, according to the regulations of evidence-based medicine.

The highly detailed analysis of the indications of hadron therapy in general and carbon ion therapy in particular performed by ETOILE and ENLIGHT have provided a ***rigorous application framework*** in which these treatments are effective solutions, probably more efficient than conventional radiotherapy. Thanks to its high, or even very high, improvement and recovery rates, the ***overall cost of treatment for the diseases should be neutral***, or even better than the pre-existing situation. Studies must be conducted, firstly to provide additional statistical evidence of this performance, and also to define more precisely the conditions for its efficiency; efforts must be made to maintain this even though carbon ion therapy's indications will gradually increase (prospective indications). Interestingly, on the basis of comments by Noël Renaudin[24] the "societal burden" of hadrontherapy in terms of the cost of health care remains moderate.

[24] Noël Renaudin (CEPS): " Stop à la flambée des prix ! " (*"Stop the price explosion!"*)
http:/www.pharmaceutiques.com/archive/une/art_1234.html

Appendix: List of Experts Who Participated in Researching Indications

The actual forms of participation are as follows:

- ***Study coordination (names underlined)***
- ***Participation in the Medical Committee (first phase) on Potential Indications (April 2002 to February 2003)***
- ***Participation in the Medical Committee on Hadron Therapy France (second phase) (May 2004 to 2010): groups on ENT, sarcomas, brain tumours, thoracic tumours, prostate tumours, digestive tract tumours, paediatric tumours, endocrine and rare tumours***
- Other types of participation such as the one-day survey (epidemiological study), organisation of local information meetings, etc. have not been included.

Specialist field	Rhône-Alpes			Paris	Rest of France, overseas
	Lyon University Hospital	**CLB**	Grenoble University Hospital ***St Etienne University Hospital***		
Radiotherapy	A Dhombres V Favrel P Romestaing	*P Pommier* *C Carrie* I Martel-Lafay *MP Sunyach* *X Montbarbon*	***Grenoble:*** J Balosso M Bolla P Fourneret **St Etienne:** *G de Laroche* ***N Mottet***	*P Bey (Curie)* *J-L Lagrange (Créteil)* *JJ Mazeron (Orsay)* P Giraud (Curie) ***C Le Pechoux (IGR)***	***JP Gérard (Nice)*** ***MH Baron (Besançon)*** ***N Breteau (Orléans)*** ***G Truc (Dijon)*** ***P Chauvel (Nice)*** ***V Grégoire (Louvain)*** ***D Weber (Geneva)*** ***F Lorchel (Besançon)*** ***P Van Houtte (Brussels)*** ***Y Lievens (Brussels)***
Brain tumours and meningiomas	**J Isnard** ***J Honnorat*** ***E Jouanneau***	***D Frappaz***	***E Gay (Grenoble)***	***H Duffau (Pitié)*** ***P Varlet (Ste Anne)***	***JP Lemaire (Bordeaux)*** ***G Noel (Strasbourg)***
Pulmonology	***M Pérol*** ***P-J Souquet*** ***B Guibert***			***D Grunenwald (Montsouris)*** ***MF Carette (Tenon)*** ***H Foehrenbach (V de G)*** ***Marine Soret (V de G)***	***A Depierre (Besançon)*** ***Anne Devillers (Rennes)***
Sarcomas	***J-Y Blay***		*F Ringeisen* (Grenoble)	***A Le Cesne (IGR)*** ***S Bonvalot (IGR)***	***G Kantor (Bordeaux)***
ENT	*M Poupart* ***P Céruse*** ***L Thomas*** ***P Breton***	*P Zrounba*	**E Reyt** *(Grenoble)*	***C Beauvillain (Montreuil)*** ***B Barry (Bichat)***	***J-L Lefebvre (Lille)*** ***G Calais (Tours)*** ***D de Raucourt (Caen)*** ***M Lapeyre (Nancy)***
Gastroenterology	***C Lombard-B*** ***Ph Merle***	***F Desseigne*** ***M Rivoire***	**Grenoble:** *J-M Phelip* *C Rebischung* *J-L Faucheron* *C Letoublon*	Ch Louvet (Saint-Antoine)	*M Macia (ICO,* Barcelona)
Paediatrics	*P Froehlich*	***C Bergeron***	***D Plantaz (Grenoble)***	**C Alapetite (Curie)** J-L Habrand (IGR)	***A Laprie (Toulouse)***
Urology		*J-P Droz* *A Fléchon*		***A Vieillefond (Cochin)***	***D Schulz-Ertner (Heidelb.)*** ***D Cowen (Marseille)*** ***F Guedea (Barcelona)***
Rare and endocrine tumours	*B Rousset* *J Trouillas* *B Hughes* F Borson-Cahzot G Raverot	***I Ray-Coquard***	*O Chabre* (Grenoble)	A-P Gimenez-Roqueplo (HEGP)	X Muracciole (Marseille)
Other	*JP Boissel; E Amsallem;* P Toutenu; D Maucort-B*;* Y Hu; G Vogin				
*Overall total **100:***	*28*	*13*	*14*	*20*	*25*