ETOILE Project:

Rapport LYCEN 2002-01 (A, B, C).
Université Claude Bernard Lyon 1
CNRS/IN2P3/IPNL
Bâtiment Paul Dirac
4 rue Enrico Fermi
Campus de la Doua
F-69622 Villeurbanne Cedex

Rapport DAPNIA – 02-06
DAPNIA, CEA/DSM/Saclay
F-91191 Gif sur Yvette

Project summary

Volume 1:
Medical and economique aspects.
Associated research

Volume 2:
Preliminary technical design

ETOILE Project:

European Light Ion

Oncological

Treatment Centre

VOLUME 1 :
Medical and economic aspects
Associated research

• Preface •

The Université Claude Bernard Lyon 1 took the initiative in 1999 to ask a number of physicians and physicists to draw up a specification for the creation of a Light Ion Hadrontherapy Centre. Under the auspices of this university and with the financial support of the local authorities and the Ministry for Research a preliminary design was undertaken corresponding to this specification. The technical part of this design was the subject of a research contract between the University (UCBL), the Commissariat à l'Energie Atomique (CEA-DSM) and the Centre National de la Recherche Scientifique (CNRS-IN2P3).

This report is thus the result of close collaboration between physicians (oncologists and radiotherapists) and medical physicists from Lyon and Grenoble University Hospitals and Regional Anticancer Centre Léon Bérard (Lyon), scientists (physicists, computer scientists and health economists, from the universities of Lyon and Grenoble) and engineers specializing in accelerators (CEA, IN2P3, CERN, GSI, TERA). Together they constitute a substantial multidisciplinary team capable of defining the structure and cost of the project, recently named ETOILE, and of initiating the research programmes necessary to perfect this innovative therapy.

This project has taken full account of the experimental work carried out in Japan and Germany. It is part of a coordinated European approach, with similar projects developed in Germany, Italy, Sweden and Austria. Clearly the result of the conjunction of the research and clinical worlds, its future will include being taken on by the national health system and the involvement of national and regional decision-makers.

This study:
• was set up under the project managership of the Université Claude Bernard Lyon 1 (UCBL), which initiated the project,
• involves physicians, medical physicists, scientists and engineers from: UCBL, Université Joseph Fourier Grenoble 1, the University Hospital (Hospices Civils de Lyon) in Lyon, the University Hospital in -Grenoble, the Regional AnticancerAnticancer Centre Léon Bérard in Lyon, the Orsay and Nice proton-therapy centres, CNRS, CEA, CERN, GSI (Darmstadt), TERA (Milan), ESRF (Grenoble) and GANIL (Caen),
• is the subject (for the technical part) of a research contract between UCBL, CNRS/IN2P3 and the CEA/DSM,
• has been funded initially by the Rhône-Alpes Region, the Metropolitan Authority of Lyon, ANVAR and UCBL, and then in the context of the "Hadrontherapy" budget of the current State-Regional Spending Plan (Ministry for Research, Rhône-Alpes Region and Metropolitan Authority of Lyon).

The following people have been involved in the preparation of this document

Steering committee
Jean Pierre Gérard (Regional Anticancer Centre A. Lacassagne, Nice) medical director of the project
Joseph Remillieux (UCBL/IPN Lyon) physics director of the project
Joël Rochat UCB Lyon (UCBL) project manager
François Dupont/Marcel Lieuvin (CNRS/IN2P3 department)
Yves Terrien (CEA/DSM department)

Medical study group
Jacques Balosso University Hospital, Grenoble
Michel Bolla University Hospital, Grenoble
Chantal Ginestet CLB Lyon
Jean-Yves Giraud University Hospital,Grenoble
Patrice Jalade University Hospital,Lyon
Alejandro Mazal Institut Curie Paris
Jean-Claude Rozenwald Institut Curie Paris
Pascal Pommier Regional Anticancer Centre, Lyon
Dominique Sappey-Marinier CERMEP/UCB Lyon

Technical study group
Jean-Marie De Conto CNRS/IN2P3 ISN Grenoble, technical project manager
Marcel Bajard CNRS/IN2P3 IPN Lyon, joint technical project manager
Rodolphe Antoni CEA/DEN/SAC/DSP/SPR Saclay
Patrick Ausset CNRS/IN2P3 IPN Orsay
Laurent Bourgois CEA/DEN/SAC/DSP/SPR Saclay
Jean Michel Buhour CNRS/IN2P3 IPN Orsay
Olivier Delferriere CEA /DSM/DAPNIA/SEA Saclay
Denis De Menezes CEA /DSM/DAPNIA/SEA Saclay
Michel Fruneau CNRS/IN2P3 ISN Grenoble
Jean François Gournay CEA /DSM/DAPNIA/SIG Saclay
Jean Luc Jannin CEA /DSM/DAPNIA/SEA Saclay
Jean Michel Lagniel CEA /DSM/DAPNIA/SEA Saclay
Bernard Launé CNRS/IN2P3 IPN Orsay
Alain Le Gendre CNRS Paris
François Méot CEA /DSM/DAPNIA/SEA Saclay
Nelly Rouvière CNRS/IN2P3 IPN Orsay
Armand Sinnana CEA /DSM/DAPNIA/SEA Saclay
Pascal Sortais CNRS/IN2P3 ISN Grenoble
André Tkatchenko CNRS/IN2P3 IPN Orsay

Scientific study group
Michael Beuve UCB Lyon/LIGIM
Flavien Brossard UCBL/IPN Lyon
Jean-Pierre Claveranne UJM Lyon/LASS
Yves Déclais CNRS/IN2P3 IPN Lyon
Albert Demeyer UCB Lyon/IPN Lyon
Florent Dupont UCB Lyon/LIGIM
Gérard Duru UCB Lyon/LASS
André Emsallem UCB Lyon/IPN Lyon
Fabien Feschet UCB Lyon/LASS
Fabrice Jaillet UCB Lyon/LIGIM
Guillaume Largeron UCB Lyon
Christophe Pascal UJM Lyon/LASS
Behzad Shariat UCB Lyon/LIGIM

Secretarial support
Jocelyne Charnay CNRS/IN2P3 IPN Lyon
Marie Louise Lombard CNRS/IN2P3 ISN Grenoble

Acknowledgements

Ministry for Research
Ministry of Employment and Solidarity
Ministry of Industry
Rhône-Alpes Region
Metropolitan Authority of Lyon
UCB Lyon chair
UJF Grenoble chair
Management of CNRS/IN2P3
Management of CEA/DSM
Management of CEA/DSM/DAPNIA
Management of IPN Lyon
Management of ISN Grenoble
Management of IPN Orsay
Management of Hospices Civils de Lyon
Management of University Hospital Grenoble
Management of Centre Léon Bérard Lyon
Management of Hôpital du Vinatier Bron
Management of CERN
Management of ANVAR Rhône-Alpes

As well as Messrs:
Tsujii (NIRS-Chiba)
Amaldi, Crescenti, Gramatica, Pullia, Rossi (TERA Foundation)
Eickhoff, Haberer, Henning, Kraft, Krause, Schlitt, Steiner (GSI)
Bryant, Détraz, Grüber, Hoffmann, Hübner, Kahle, Thivent (CERN)
Palanque (CEA)
Ferrand, Meyroneinc (CPO)
Bouteille, Hardy, Jacob, Magnien (ESRF)
Baron, Berthe, Petit, Rannou (GANIL)
Poizat (IPNLyon)
Mongereau (INSA Lyon)

Foreword

Successful treatment of cancerous tumours frequently involves irradiation. This is most often performed using X rays, but also, more rarely, using proton beams (proton-therapy) or neutron beams (neutrontherapy). One method, light ion hadrontherapy, has been tested in Japan and Germany for several years. This method, which requires heavy-duty equipment, has demonstrated the advantage of these ions, and in particular carbon ions, for the accurate treatment of deep-seated tumours which are inoperable and radioresistant.

The French ETOILE project: Espace de Traitement Oncologique par Ions Légers Européen (European Light Ion Oncological Treatment Centre) proposes to build a carbon ion hadrontherapy centre in the Rhône-Alpes region of France. This project is based on the promising clinical results obtained recently at Chiba in Japan and Darmstadt in Germany, following on from the pioneering work initially carried out at Berkeley in the USA. We are not the only organization with this aim, as a fairly similar development will be initiated shortly in Heidelberg, Germany, and projects at a similar stage as ours are in preparation in Milan, Stockholm and Vienna. The emergence in Europe of a number of projects collaborating with one another in a network is absolutely necessary for the clinical validation of treatment using carbon ions.

We are convinced that France has the resources to develop such a centre, which will be able to cure more than 500 of the 1000 patients treated each year (for whom existing treatments would have little effect). This will help to put France back in the market for heavy-duty equipment for medicine. This aim is economically viable in that the cost of treatment is lower than other cancer therapies currently in use.

The French project will be located in Lyon, in the Rhône-Alpes region. This decision is justified both by the strong initial commitment of the Claude Bernard and Joseph Fourier scientific and medical universities at Lyon and Grenoble respectively. In addition, Geneva the home of CERN where the study of a synchrotron (PIMMS) adapted to the medical requirements of hadrontherapy was carried out, is close. This project has been made possible by the tight collaboration between the French universities, the CEA (DSM) and the CNRS (IN2P3). Moreover, a European network (ENLIGHT) has recently been created to co-ordinate the essential medical and technical collaboration between the various European projects.

The multidisciplinary research programmes that have been undertaken around the ETOILE project are essential for the provision and control of treatment plans for patients. They ensure that all the clinicians, radiobiologists, medical physicists, physicists, engineers, computer scientists and economists work together. There is no doubt that if this project is a success, there will be considerable medical and economic spin-offs throughout the whole health sector, in particular in the fields of oncology, including radiotherapy, imaging and medical physics.

Contents of volume I

• I •
Introduction and global situation

Cancer, a major public health problem

1.5 million new cases of cancer appear every year in Europe. One in four people will die from cancer during the 21st century. It will be the main cause of death between the ages of 45 and 65. Even in developed countries, cancer will be the largest public health problem. In two out of three cases death is due to the metastatic spreading of the cancerous cells throughout the whole organism. Only new medical treatments, aimed at specifically targeting these cancerous cells, will be capable of eradicating the metastases. Moreover, one third of these deaths (i.e. 300,000 people in Europe) is due to inadequate local control of the tumour. Surgery remains the principal treatment for local "control". Improvements in this technique are always possible, but will never achieve 100% local control. Radiotherapy is, after surgery, the main curative treatment for cancer, and is also aimed at local control of this disease [1] [2] [3].

Radiotherapy, an effective treatment which is constantly being improved

Two out of three patients suffering from cancer are treated by radiotherapy during their illness. Radiotherapy is responsible for 30 to 40% of cures, on its own or combined with other treatments. Its action is conservative, avoiding mutilation and maintaining a good quality of life. Its cost is relatively modest, accounting for only 5% of the total expenditure on cancer treatment in France.

To date, considerable progress has been made in conformal radiotherapy and chemo-radiotherapy, and radiotherapy departments offer these techniques. In years to come, the effectiveness of treatments using photons will increase significantly as modulated intensity therapies become available. Moreover, the increasingly wide use of chemotherapy combined with radiotherapy significantly increases the effectiveness of treatment. However, a large number of tumours remain radioresistant and will result in failure of local treatment, despite the availability of improved radiotherapy treatments.

Light ion hadrontherapy is a leading edge technique which is providing a therapeutic advance in oncology

Neutrontherapy, despite a very unfavourable dose distribution, is biologically more suitable than photons or electrons for controlling certain deep-seated radioresistant tumours (cancers of the parotid gland, sarcomas). Light ions, and in particular carbon ions, should form the basis of future treatments for radioresistant tumours, as they combine the advantages of protons (Bragg peak ensuring precise dose distribution) and neutrons (high Linear Energy Transfer). These two important properties have been confirmed by the clinical results obtained in CHIBA, Japan (1100 patients) and in DARMSTADT, Germany (100 patients) [4]. The high tolerance to carbon ion treatment has now been clearly demonstrated, with less than 4% of grade III delayed toxicity, even with a 70 GyE[1] dose. The local control obtained for the various radioresistant tumours (brain, head and neck, lung, liver, sarcomas, prostate, etc) is between 70 and 90%. Irradiation by carbon ions thus seems to be a significant breakthrough in the use of radiotherapy in oncology.

The number of potential patients in France can be estimated at 18 000 a year, for whom carbon ions would provide the best potential effectiveness – as the only form of irradiation or in combination with photon irradiation. Each year, ETOILE, which plans to treat 1000 patients with radioresistant tumours, whose recovery rate with another treatment would be very low, and it is estimated that at least 500 of these patients will be cured.

France must be involved in the development of carbon ion treatment

In Japan there are currently two treatment centres using carbon ions. In Europe, five countries have similar projects. The project in Heidelberg (Germany) was definitively accepted at the beginning of 2002. France must be involved in these new developments, initially for the benefit of its own patients and then to promote this new technique which will stimulate all areas of radiotherapy, including radiobiology, the procedures and tools for treatment, dosimetry and the associated software. Lyon, at the heart of the Rhône-Alpes region, is particularly well-placed for such a hadrontherapy centre. Rhône-Alpes is a large region with six million inhabitants, and a number of university cities which are easy to reach in less than an hour. Radiotherapy is used in many of the university departments. There is close collaboration between the oncologists, radiotherapists and physicists in Lyon and Grenoble, who are also in close contact with the researchers at CERN in Geneva.

[1]Gray équivalent, with reference to treatment with the same biological effect carried out using conventional radiotherapy.

The whole of the radiotherapy community in the Rhône-Alpes region is closely connected with the French oncology network via professional associations such as SFRO[2] or the Fédération Nationale des Centres de Lutte Contre le Cancer (French National Federation of Comprehensive Cancer Centres). The ETOILE centre at Lyon will collaborate with the other European centres for carbon ion treatment through ESTRO[3] which represents a network of more than 5000 members throughout Europe (400 of whom are in France). Clinical research, which is essential for the definitive validation of this therapy, will be carried out with the collaboration of the EORTC[4].

Radiotherapy and hadrontherapy: a future of at least thirty years

Every 5 or 10 years, for the last 30 years, there is a "miracle cure" for cancer that receives lots of publicity, for example:

- adjuvant chemotherapy in	1975
- immunotherapy in	1980
- oncogens in	1985
- taxanes in	1990

For the last 10 years, it has been hoped that cell therapy and genetic treatments will provide a definitive solution. It is certain that, increasingly, we will be able to specifically target certain molecules to cancerous cells (Glivec®, Herceptin®, Mabthera®). These treatments will certainly advance over the next 10 years. It is impossible, today, to predict the progress that will be offered by gene therapy, particularly in the field of cancer. As we have seen in the past, progress in therapy is usually made very gradually, one step at a time.

In the next 30 years, together with these biological and medical innovations and those made in surgery, radiotherapy will remain one of the basic curative treatments. There is a fundamental agreement on the need to combat cancer, a cellular disease which is extremely heterogeneous, using the complementary natures of the therapeutic methods. It is certain, that each method will have its place in the future, in the face of the current rate of 140, 000 deaths each year.

Radiotherapy could be increasingly combined with medical treatments (chemotherapy, biomodulators of the p53, EGF, VEGF). Technological developments - connected with conformal radiotherapy, intensity modulated radiotherapy, and hadrontherapy (particularly using carbon ions) - will make it possible to continue to improve the effectiveness of this area of therapy in the long term, with an increasingly important attention paid to quality of life.

Arguments that will be developed in this document in favour of carbon ion hadrontherapy suggest that it is reasonable to think that in the coming 30 years this treatment will play a very important role in the curative treatment of cancers alongside other therapies.

The spin-offs from this technology for radiotherapy as a whole will also be considerable in the coming decades.

To summarise, light ion hadrontherapy, particularly using carbon ions, seems to be one of the most certain means we have of improving treatment and curing a significant number of patients with cancers, and this will play an important role for at least the next 30 years. The cost of this treatment will be reasonable. France and Europe must play a leading role in the development of this new phase in the fight against cancer.

[2]Société Française de Radiothérapie Oncologie
(French Society of Oncological Radiotherapy)
[3]European Society for Therapeutic Radiology and Oncology
[4]European Organisation for Research and Treatment of Cancer

• II •

Hadrontherapy and the treatment of radioresistant tumours. Research

II-1
Improving the therapeutic index of radiotherapy

The effectiveness of radiotherapy is limited by the risk of acute toxicity and sequels connected with the presence of radiosensitive healthy tissue or organs close to the tumour and by the radioresistance of many cancers.

The protection of healthy tissue requires improvement in the precision of radiotherapy, adapting the irradiated volume precisely to the volume of the tumour. This is "conformal" radiotherapy. Recent developments in computer science, imaging and technology have made it possible to develop the necessary methods to get closer to this objective.

Two main ways of overcoming the radioresistance of many cancers have been developed:

- The first consists of increasing the dose of irradiation delivered to the tumour. This is only possible by better protection of healthy tissue, using the complex techniques of conformal X-rays radiotherapy, and also by using the physical properties (Bragg peak) of certain particles, protons and light ions (carbon ions in particular).

- The second consists of increasing the "biological effectiveness" of radiotherapy in particular for cancers which have a low sensitivity to photons (X-rays). This involves the use of "radio-sensitizing" products and in particular chemotherapy, but above all "high Linear Energy Transfer" particles, neutrons and light ions (and in particular carbon ions). For an equivalent physical dose, the relative biological effectiveness of neutrons and carbon ions is around 2 to 3 times higher than that of photons.

These points are developed below.

II-2
Progress and limits of radiotherapy with photons

Irradiation with photons, which is the basis of external-beam irradiation, has developed over the last 100 years towards a gradual escalation in the dose. The escalation of dose was initially achieved with high energy photons used to treat deep-seated tumours with a better tolerance. The development of telecobalt devices in the 1950s, then linear accelerators in the 1970s and 1980s led, in less than 50 years, to a gradual increase in the dose delivered to the tumour from 40 to 70 Gy, while reducing the secondary effects of irradiation.

Progress in technology, imaging and computer science have made it possible, since the 1990s, to improve the definition and application of the concept of "conformal radiotherapy" for photons. The poor physical properties in terms of ballistics (precision) of photons make it necessary, for a given treatment, to multiply the incidences of irradiation (or "fields of irradiation"), each one being conformed to the "2-D" shape of the tumour seen from its focus. This makes it possible to limit and/or distribute the dose of irradiation better over the surrounding healthy tissue and to escalate the dose beyond 70 Gy.

Conformal radiotherapy has been developed in France since 1995, and has been the subject of rigorous international medical and physical evaluations in France, [5] [6] [7] [8] [9] despite a technological "lag" of almost five years compared with the major American universities. Prostate cancers have been studied in particular. The first clinical results of dose escalation (78 - 80 Gy as compared with a "conventional" dose of 70 Gy) have confirmed the advantage of high dose radiotherapy alone for cancers with an "intermediate" prognosis [10][11]. The respective advantages of hormone therapy and dose escalation for forms with a poor prognosis remain to be assessed [12]. The French teams, and in particular those in the Rhône-Alpes region, are involved in the evaluation of conformal radiotherapy for lung cancers in order to improve the definition of the volumes to be irradiated and to attempt to predict and avoid complications [13][14] [15] [16] [17] [18]. The results of dose escalation are currently much more disappointing for lung cancers, with a local failure rate of more than 60% for doses of more than 70 Gy in the irradiated area [19]. Moreover, dose escalation is not possible for a third of patients due to the unacceptable risk of pulmonary complication [20] [21]. Studies have also been carried out for cancers of the facial sinuses, cancers of the cavum, which are particularly difficult to irradiate due to the organs at risk nearby (visual pathway, salivary glands, temporo-mandibular articulations) and/or their frequently radioresistant character, also illustrating the limits of dose escalation and the clinical results, which are still disappointing [22] [23] [24].

IMRT (Intensity Modulated Radiotherapy) consists of modifying the intensity of the various sub-regions of each irradiation beam to improve the conformation of the irradiation further, in particular for concave shaped volumes. This technology was developed around 1995 in certain American universities, as well as in Germany and England. Linear accelerators and software are now on the market, with which the first French teams were equipped in 2001, again around 5 years behind the leaders. Clinical data is still limited, but an improvement, in particular in initial and long term tolerance of treatment, should be achieved, with an expected increase in effectiveness for tumours of complex shape or location, especially in the field of Head & Neck tumours [25] [26] [27] [28] [29]. It is important to highlight an important decision by the health authorities in France, which was the funding of the medico-economic evaluation of "therapeutic innovations" initiated in 2000. Conformal radiotherapy with intensity modulation is also to be the subject of a multicentre medico-economic evaluation in France, funded in the context of the 2001 national research programme of the Ministry of health and hospital management [30].

Conformal radiotherapy with intensity modulation will probably be the final step in the technological development of photon radiotherapy. These techniques will probably be routinely applied in most radiotherapy centres in the next 5 to 10 years, and will become the reference treatment for many tumours [6].

II-3
Advantages of hadrontherapy

II-3-1 Protons

At the same physical dose protons have the same biological effectiveness as photons or electrons. Their only advantage is a ballistic advantage, characterised by the Bragg peak.

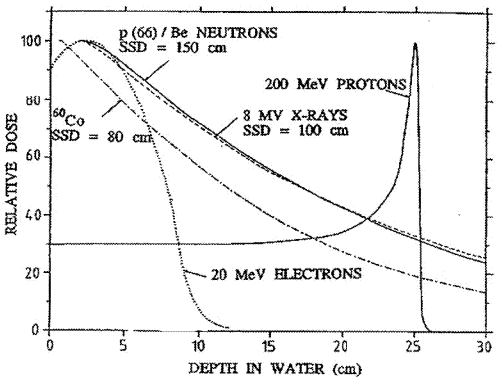


Figure II-1: comparison of doses delivered by protons (Bragg peak), photons and electrons

There are about fifteen installations in the world, two of which are in France, at Nice (Medicyc) and Orsay (CPO). In the USA, two major centres are already in operation and three are being created.

The indications which have been validated [31] are choroidal melanomas (eye) (treated in Nice and Orsay) [32] and tumours of the skull base (chordomas, chondrosarcomas) treated in Orsay [33]. When the characteristics of the beam allow it, other types of cancer can be treated, in particular cancers of the prostate, but only preliminary results are available [34] [35] [36] [37].These latter indications are not currently covered in France. Since the potential benefit of protontherapy is based on its ballistic properties (Bragg peak), the permanence of their advantage in relation to conformal IMRT photontherapy should be confirmed in comparative studies. However, it may be considered that the results of conformal radiotherapy and intensity modulation for photons will be, in certain fields, similar to those for protons, since the dose distribution will be fairly similar, with a similar biological effect.

II-3-2 Neutrons

These are particles with a high Linear Energy Transfer (LET), which gives them specific biological properties. The main drawback of neutrons is their poor ballistic quality (similar to that of cobalt 60 photons) which makes precise high dose irradiation of the tumour difficult without irradiating the surrounding healthy tissue at toxic doses.

The clinical results concerning the use of neutrons in oncology show the advantage of projectiles with a high irradiation density (high LET) for the treatment of certain hypoxic or slow-growing cancers. Indications which have currently been validated are cancers of the salivary glands and inoperable soft tissue sarcomas [31] [38] [39]. For locally-advanced prostate cancers, the results from randomised studies have demonstrated a greater efficacy of neutrons (alone or combined with photons) in comparison with "conventional" techniques of radiotherapy using photons only [40]. For advanced cancers in the head and neck region, a randomised study has also demonstrated a significant improvement in local control in favour of neutrons, but at the expense of an unacceptable toxicity [41]. Other small-scale comparative studies have not been able to demonstrate a therapeutic advantage due to inadequate doses and/or major toxicity [42] [43] [44].

Boron neutron capture therapy (BNCT) is a complex technique based on the ability of a boron isotope (10B) to capture thermal neutrons. It is currently being tested in Europe at a single site in Holland, at the Petten high flux reactor within a nuclear research installation. The efficacy and safety of this technique is currently being evaluated by EORTC for certain cerebral tumours (glioblastomas) [45].

II-3-3 Light ions

These are electrically charged particles with a greater molecular mass than protons and neutrons, which gives them their **ballistic and biological** properties which are very advantageous in radiotherapy [46].

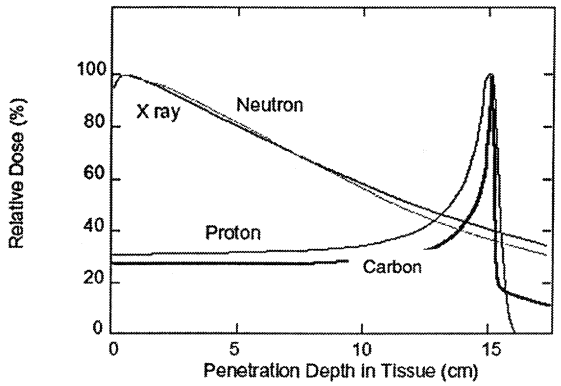


Figure II-2 : proton and carbon Bragg peaks (J. Alonso)

Their ballistic properties are even better than those of protons (narrower Bragg peak and smaller lateral diffusion). With a high LET, and thus, a high ionization density, they also have the biological advantages of neutrons, i.e. a **high Relative Biological Effectiveness** (RBE between 1.5 and 2.5) and a very low **Oxygen Enhancement Rate** (OER). Schematically, an RBE of 2 means that at an identical physical dose (to that of photons), the biological effect of carbon ions is twice as effective. This relative biological effectiveness is a complex spectral multiparameter measurement.

Two phenomena significantly modulate the RBE throughout the trajectory of carbon ions. On one hand the LET – RBE relationship means that the RBE increases gradually just like the LET throughout the trajectory to reach its highest values in the Bragg peak (Figures II-3 and II-4) where the LET is represented by average values because the spread out Bragg peak consists of a spectrum of particles with different LETs. Thus, at the start of the trajectory in healthy tissue the LET and RBE are low and they increase in the Bragg peak and thus in the tumour. This explains the "biological" dose advantage of carbon ions in the tumour, in comparison with protons, while delivering the same 'biological' dose in the entry track (Figure II-5). Moreover, since the RBE is a relative biological characteristic, it is dependent on the biological effects used as reference. The short and long term antitumoural effect and toxic effects on healthy tissue have different RBE values for the same LET. The antitumoural RBE, in certain conditions, can be higher than the toxic RBE so that the therapeutic advantage may be increased further in comparison with that expected for the physical doses. Therefore, there is a spectrum of RBE values in the whole of the irradiated volume. The RBE must therefore be modelled using the physical parameters (depth, density and LET) and biological parameters (type of tissue, biological effects taken into account) in order to establish a planned dosimetry, a biological dosimetry, which is the only one valid for carbon ions. This modelling is very complex and must also take hypoxia into account. It represents the main radiobiological and bio-mathematical challenge to the clinical use of carbon ions [47] [48] [49].

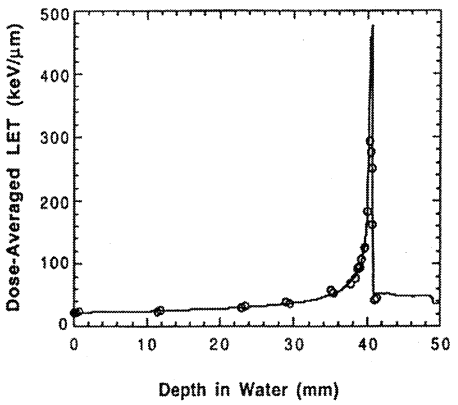


Figure II-3 : distribution of the LET in water (dose-averaged LET) of carbon nuclei 135 MeV/u. Lines = theoretical value, m = experimental measurements (T. Kanai et al [50])

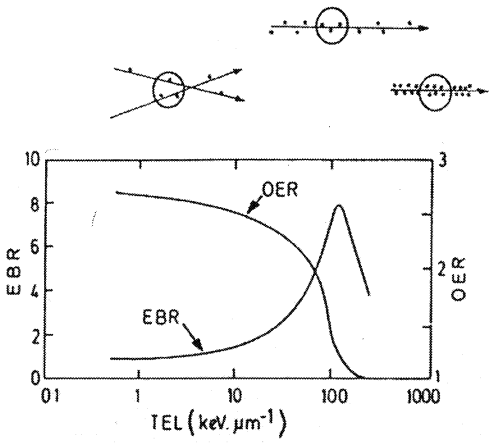


Figure II-4: relationship between the LET and the relative biological effectiveness (RBE) and the oxygen enhancement rate (OER). (M Tubiana et al [51])

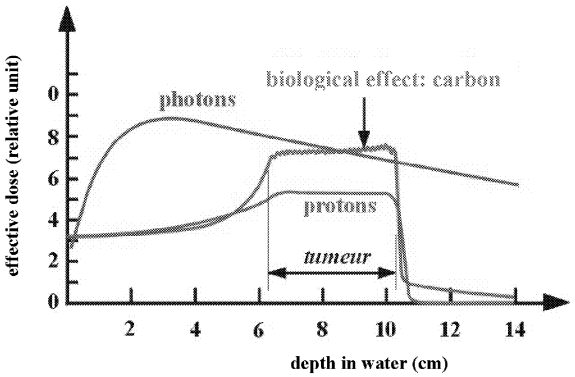


Figure II-5: spread out Bragg peaks

The results from laboratory experiments, but also clinical experiments on human cancers at Chiba (Japan) and Darmstadt (Germany) confirm that carbon ions, due to their biological properties, are particularly effective for treating radioresistant tumours. This is particularly true for hypoxic tumours since the increase in the LET is also connected with a important property of ions (and also of neutrons), i.e. the elimination of radioresistance connected with hypoxia (OER), a major reason for therapeutic failure in radiotherapy (figure II-4).

The knowledge accumulated with neutrons makes it possible to evaluate precisely the risks of toxicity with particles with a high LET, in particular carbon ions. For the treatment of radioresistant tumours, carbon ions are a good compromise between the need for a high LET (which increases with Z) and the phenomenon of fragmentation of the ion in matter (which increases with A) and decreases the ballistic quality.

The combination of a very strong biological effectiveness and high ballistic precision makes the large decrease in the cell repair phenomenon useful in clinical practice and thus reduces the differential effect between healthy and cancerous tissue which is unfavourable in radioresistant tumours [52] [53]. This theoretically establishes particular indications for carbon ions [51] and also makes it possible, as the results from Chiba [54] have shown, to reduce the number of irradiation sessions with carbon ions, thus simplifying the logistics of treatment.

In summary, light ion beams and more particularly carbon ion beams provide an optimum combination of all the favourable characteristics that are currently known for the effectiveness of anti-cancer radiotherapy.

These characteristics are the ballistics of the spread out Bragg peak, the high RBE and the low sensitivity to the oxygen enhancement rate. The overall efficacy of such particles is an order of magnitude greater than that of photons. Such progress has rarely been achieved in radiotherapy in a single step and leads to hope for a veritable therapeutic advance in the local control of tumours. Carbon ions are therefore the most effective beams for irradiating tumours which are currently resistant to conventional treatment using photons or electrons.

II-4
Current medical data for carbon ion hadrontherapy

A recent literature review of the medical data concerning hadrontherapy (protons, neutrons, light ions) suggests that it is beneficial in certain indications [35]. The purpose of this section is to give details of the current results for light ions, and in particular for carbon ions.

More than 1200 patients have been treated by carbon ion hadrontherapy since 1994 in Chiba and GSI. This experience comes both from a medical centre dedicated to cancer treatment, at the National Institute for Radiological Science (NIRS) in Chiba, Japan (with about 1000 patients treated since 1994), and from a nuclear physics research centre (containing an installation for medical purposes) located at the GSI in Darmstadt, Germany (with about 100 patients treated since the end of 1997). A much earlier experiment had been carried out by the pioneering centre of the Lawrence Berkeley Laboratory in California in which 2487 patients were treated between 1957 and 1993 with light ions (mainly helium, as well as neon and carbon).

II-4-1 Lawrence Berkeley National Laboratory (USA)

The first treatments, carried out in the context of a research laboratory, the Lawrence Berkeley National Laboratory (USA) involved 30 patients treated with protons between 1954 and 1957. Then 2054 patients were treated with helium up to 1987, and finally 433 patients with neon and carbon ions from 1975 to 1993. Excellent results for 5-year relapse-free survival were published for meningiomas (85%), chondrosarcomas (78%) and chordomas (63%) [46] [55] [56]. A non-randomised comparative study demonstrated the superiority of light ions in comparison with photons in the post-operative irradiation of cholangiocarcinomas [57]. In addition to this data on effectiveness, the experiment at Berkeley demonstrated the feasibility and safety of light ion hadrontherapy for humans.

II-4-2 National Institute for Radiological Science (NIRS), Chiba - Japan

In 1994 the NIRS was the first medical centre dedicated to the treatment of cancers using carbon ions. Three treatment rooms were set up, with fixed beams only (two rooms with a horizontal beam and one with a horizontal and a vertical beam). Numerous cancer locations were treated following rigorous clinical research protocols. The principle of the NIRS was to carry out irradiation with carbon ions only. These studies had the initial objective of escalating the irradiation dose (up to a photon biological equivalent of 95 Gy for lung cancers), and then for other locations, assessing hypofractionation (i.e. reduction of the number of irradiation sessions needed for the treatment) with carbon ions ("phase I trials"). Specific irradiation protocols were defined, and these are still being evaluated on a growing number of patients treated in a homogeneous manner ("phase II trials"). Comparative studies with protons are planned in the next few years ("phase III trials"). Currently in Japan, tumours with a low level of radiosensitivity and less than 3 cm in diameter are treated in priority with protons, while larger tumours and in particular adenocarcinomas are treated in priority with carbon ions. In both situations either the tumour is not suited for resection or the patient is inoperable.

The first results were published in 1998 at the 6th International Congress on Progress in Radiotherapy [58]. More recent results were presented by Prof. Tsujii at a meeting organised at the Hôtel de Ville in Lyon [4] and presented and published at the European radiotherapy congress of ECCO held in 2001 [59] [60].

The clinical results from 1042 patients are available:

- Lung cancers (18% of patients)
  The dose delivered was progressively increased from 60 to 95 GyE (biological equivalent of irradiation by photons). A relationship dose-effect was observed. At the same time, the number of fractions needed for the treatment (and the total duration of the treatment) was progressively reduced from 18 fractions (in 6 weeks) to 9 fractions (in 3 weeks) and to 4 fractions now. Local control at two years for localised stage I tumours (evaluation by MRI and PET scan) was 86%, with less than 5% of severe complications (radiation pneumopathy).

- Inoperable cancers in the head and neck areas (stages III-IV) (17% of patients)
  These were mainly cancers of the facial sinuses (squamous cell carcinomas, adenocarcinomas, cystic adenoid carcinomas and melanomas), and certain squamous cell cancers of the upper respiratory tract. In the whole series the local control was 62% at two years, but the efficacy was much higher for certain radioresistant cancers (cystic adenoid carcinomas, melanomas, adenocarcinomas) with 100% local control at 2 years.

- Hepatocarcinomas (11%)
  Liver cancer is an important public health pro-

blem in Japan. Studies have shown that it is possible to reduce hypofractionation in 15 fractions (5 weeks of treatment) to 4 fractions (one week). For inoperable cancers, the local control at two and three years was 80%.

- T2-T3 prostate cancers (14%)
  The treatment for these patients included initial hormone therapy, followed by 20 sessions of irradiation over five weeks with an escalation then a progressive de-escalation of the dose (66 GyE) as a function of the clinical results. The local control rate at two and three years, evaluated on biopsies, was 100%.

- Inoperable sarcomas (6%)
  These patients had spinal or paraspinal sarcomas (33%), pelvic sarcomas (56%) and more rarely sarcomas of the extremities (11%), with a median volume of 560 cm^3 (20-2290 cm3). The dose was escalated from 53 to 74 GyE, in 16 fractions over 4 weeks. The local control at three years was 73%, and the overall survival rate only 46% at 3 years due to the appearance of metastases. A significant dose-effect has been demonstrated (local control at 3 years: 82% as opposed to 52% for doses of 64 GyE or more).

- Other cancers (uterus, brain, oesophagus, pancreas, rectum, etc) It is not possible to analyse the effectiveness due to the small number of patients.

Table II-1: shows the local control rates for patients treated with carbon ions only. Treatments at Chiba between June 1994 and February 2001 ([59] [61] and personal data from Prof. Tsujii).

Localisation *(phase)*	Dose *(in GyE)*	Number of fraction / Duration in weeks	% local control at: *(number of patients)*		
			1 year	2 years	3years
H&N[1] (I)	48.6 - 70.2	**18**/6	85 *(13)*	80 *(8)*	80 *(8)*
H&N[1] (I)	52.8 - 64	**16**/4	80 *(15)*	71 *(15)*	67 *(12)*
H&N[1] (II)	57.6 - 64	**16**/4	83 *(83)*	62 *(52)*	52 *(27)*
Lung[2] (I)	59.4 - 95.4	**18**/6	94 *(48)*	62 *(47)*	57 *(44)*
Lung[2,4] (I)	68.4 - 79.2	**9**/3	91 *(34)*	86 *(28)*	75 *(16)*
Lung[2, 4] (II)	72	**9**/3	100 *(39)*	-	-
Sarcomas[3] (I)	52.8 - 73.6	**16**/4	88 *(64)*	76 *(46)*	68[5] *(22)*
Liver[3] (I)	49.5 - 79.5	**15**/5	95 *(22)*	79 *(19)*	75 *(16)*
Liver[3] (I)	48 - 69.6	**12**/3; **8**/2; **4**/1	94 *(71)*	83 *(42)*	79 *(34)*
Prostate[3] (I)	54 - 72	**20**/5	100 *(34)*	100 *(33)*	100 *(30)*
Prostate[3] (II)	66	**20**/5	100 *(72)*	100 *(31)*	100 *(18)*
Uterine cervix[3] (I)	52.8 - 72	**24**/6	53 *(30)*	50 *(28)*	42 *(26)*
Uterine cervix[3] (II)	68.8 – 72.8	**24**/6	79 *(14)*	58 *(12)*	-
Astrocytoma G2 (I)	50.4 – 55.2	**24**/6	73 *(11)*	50 *(10)*	22 (9)
Glioblastoma (I)	66.8 – 72.4	**33**/7	42 *(36)*	17 *(23)*	16 (21)
Skull base (I)	48 – 57.6	**16**/4	100 *(14)*	89 *(9)*	-

GyE (Gray equivalent)

Table II-1: local control rate for patients treated with carbon ions only at Chiba (Japan)

1 inoperable locally advanced head and neck (H&N) squamous cell carcinoma, or cystic adenoid carcinoma, melanomas, adenocarcinomas of the facial sinuses
2 stage I pulmonary carcinoma
3 inoperable locally advanced tumours
4 initial staging by PET Scan
5 82%, if the doses are 64 GyE or more

II-4-3 Gesellschaft für Schwerionenforschung (GSI) Darmstadt - Germany

Clinical research at GSI has been carried out in the context of a research laboratory which provides a "medical line" three to four months a year for the treatment of cancers. The facility only has one treatment room with a horizontal beam. The first treatment was carried out in December 1997, and more than 100 patients have now been treated.

The experience at the GSI, in terms of choice of indications and technological and medical development, is different from that of the NIRS. Making use of the earlier experience, but limited by the availability of the treatment room and a single fixed horizontal beam, this group has prioritised indications of slow-developing, highly radioresistant tumours of the skull base and sinuses. Certain patients have been irradiated with carbon ions only, while others have received a combination of photons and carbon ions. At the same time, this group has developed more advanced techniques than those of the NIRS for irradiation and quality control: raster scanning, equivalent biological dose planning and "in situ" PET scan in the treatment room.

There are initial reports of two patients successfully treated at three and five years, after failure of photon irradiation (chordoma, cancer of the cavum).The first results were published in 2000, and concern the first 45 patients treated for cancer of the skull base [63]. Of these, 27 patients who had a chordoma or a chondrosarcoma were treated with carbon ions only (60 GyE in 20 sessions), 18 patients with another type of tumour received a combination of photons (45-50 Gy in 25 sessions) and carbon ions (15 to 18 Gy in 5 to 6 sessions). The control rate at one year was 94% (no recurrence in the irradiated volume), with no severe toxicity. Clinical results for chondroma and chondrosarcoma were updated and published in 2002. Thirty seven patients were irradiated with carbon ion only. With a 13 months mean follow-up local control was obtained in all patients, but 2. In these 2 cases, recurrence occurred outside the treated volume.

II-4-4 Synthesis of previous experiments
The following lessons can be learned from these experiments:
For the Japanese patients, a broad study of the potential indications was carried out in the Japanese epidemiological context. This explains the large number of locations treated. Nearly 90% of the treatments were carried out on a dozen different indications, with four main indications: bronchial cancer (18%), head and neck cancers (17%), prostate cancers (14%) and primary cancer of the liver (11%). The Japanese context explains why cancers of the liver are to be found among these indications, as it is very common in Japan. This body of data makes it possible to make an initial selection of indications based on the results presented by the NIRS

The experience at the GSI in terms of choice of indications and technological and medical development is different. Making use of earlier experience, but being limited in terms of beam availability, this group prioritised indications of slow-developing, highly radioresistant tumours of the skull and face with remarkable success and excellent tolerance. The work performed at GSI has, also, enabled significant advances to be made in the technological and computing fields.

The aim of the French project is to generalise and develop the German technological experience and apply it to therapeutic indications not limited to the head, but covering the whole body, for radioresistant tumours for which local control represents the main condition for recovery. The aim of all the other European projects is the same.

II-5
Definition of the indications of carbon ion hadrontherapy in oncology

The number of cases of cancer in France for which carbon ion hadrontherapy could potentially be indicated is estimated to be 18,000. A detailed study is to be carried out in 2002 in consultation with the other European teams and the Japanese specialists to set up a common medical project.

II-5-1 Introduction
The general selection criteria for indications have been defined using the current data. These indications, which have been defined for hadrontherapy, may change or increase in number over time. It is certain that the experience acquired, increased accessibility to hadrontherapy centres and also progress made in global screening and treatment of cancer, will increase the demand for such treatments.
It is currently estimated that around one third of deaths from cancer are connected with failure of existing local treatments such as radiotherapy and therapeutic combinations, in particular chemo-radiotherapy. The importance of local control for curing tumours will increase with the progress made in treatment of metastatic disease, since this currently conceals many local failures [64].

"Medical" oncology research is moving towards greater specificity of drugs (monoclonal antibodies, possible gene therapy, etc) which should improve efficacy and provide better tolerance of treatments, particularly for metastases, which are less heterogeneous than the primary tumour. Early detection of tumours will reduce the risk of metastases and thus necessitate greater efficacy and lower toxicity of local treatments. Therapeutic combinations and a multidisciplinary approach to the treatment of cancers should therefore continue.

"Poly-radiotherapy", the combination of photons and carbon seems particularly advantageous in certain clinical situations, where a "subclinical" tumour volume requiring moderate doses of irradiation could easily be treated with photons by the radiotherapist nearer to the patient's home, the patient then being referred to the hadrontherapy centre for a short period (less than 10 days) to receive additional very focused treatment with carbon ions.

In addition to the medical data, the medical project must include epidemiological data on the targeted cancers (potential recruitment) and the number of sessions possible in the planned configuration (three rooms) according to the operating scenario.

II-5-2 Selection criteria for carbon ion hadrontherapy

For the patient
- general and psychological condition compatible with the treatment
- no associated disease affecting the short term vital prognosis

For the tumour
- tumour for which the best existing treatments have a high local failure rate due either to the resistance of the tumour, or its location close to very sensitive organs which cannot be adequately protected by conventional techniques

- disease limited to the locoregional stage and with low metastatic potential
- disease for which the metastatic spread can be effectively controlled on a long-term basis by pharmacological treatments

For the treatment

- imaging and medical data enabling the precise definition of the anatomo-clinical target volume (cancer and subclinical spread)
- immobilisation system for the precise positioning of the patient
- ability to locate precisely the target volume, if it is immobile, or to take into account or control the internal movements of the patient during treatment, if it is not.
- restriction to anatomical locations of the tumour which are compatible with the ballistics of carbon ion beams (for an installation which does not have a gantry).

II-5-3 Proposed indications

II.5.3.1 Tumours which are rare, radioresistant and in difficult locations

These tumours will represent around 25% of cancers treated. The treatment will mainly be carried out using carbon ions only.

- Tumours of the skull base and spinal and paraspinal tumours all histological types, except lymphomas
- Low grade sarcomas inaccessible to neutrons which cannot be excised or can only be partially excised
- Tumours of the salivary glands inaccessible to neutrons
- Low grade gliomas
- anaplasic cancers of the thyroid
- Tumours of the facial sinuses melanomas carcinomas which cannot be excised
- Tumours of the pituitary gland
- Paediatric cancers
- Local recurrence in irradiated areas (adenocarcinoma of the rectum, etc)

II.5.3.2 Common radioresistant tumours

These tumours must be the subject of the most comprehensive possible report on their local, glandular and metastatic spread, in order to specify the volumes to be treated and, optionally propose combined treatments, or even contra-indicate carbon ion treatment, in the case of metastatic spread which cannot be controlled by medical treatments. Combinations of photons and carbon ions will be discussed according in particular to the risk of glandular spread. Prospective randomised studies with conformal protontherapy techniques will be plan ned for the early years of development.

- Hepatocarcinomas
- Adenocarcinomas of the pancreas and the bileducts which cannot be excised, are localised and are developing slowly
- Non-small cell lung cancers
  - stages I – II with mediastinal glandular evaluation
  - stage IIIA with metastatic evaluation++
- Locally advanced tumours with low metastatic potential
  - stage III cancer of the uterine neck
  - stage III-IV Head & Neck squamous cell carcinomas
- Tumours for which the curative treatment should be surgical (tumours which are not very radiosensitive) but for which surgery is contra-indicated for medical reasons
  - adenocarcinoma of the rectum
  - adenocarcinoma of the endometrium
- Cancers of the bladder
- Primary brain cancers
- Cancers of the cavum which have spread to the skull base
- Prostate cancers (T3-T4 locally advanced, non metastatic)

II-5-4 Estimate of the potential populations

II.5.4.1 Cancer in France: incidence, mortality, premature mortality and relative survival
The French epidemiological data has been obtained from the French cancer registers (located in the following departments: Calvados, Côte d'Or, Doubs, Isère, Somme). The survival data ([65] and table II-2) were estimated from 25,319 observations between 1985 and 1994 (14,783 men and 10,536 women).

Cancer	Number (incidence)	Deaths (rate)	(rate)	Early deaths	Relative survival (%) (CI 95%) 1 year	3 year	5 year
Oral cavity, pharynx	13.332 (22.98)	4976 (8.58)	2834 (5.74)		73	45	38 (32-44)
Œsophagus	5361 (9.24)	4596 (7.92)	2024 (4.10)		40	12	9 (7-11)
Stomach	7838 (13.51)	5809 (10.01)	1113 (2.26)		47	29	25 (23-28)
Colon / Rectum	31, 495 (54.28)	15, 322 (26.41)	2999 (6.08)		75	58	51 (49-54)
Liver	4266 (7.35)	6312 (10.88)	1793 (3.63)		24	12	8 (5-11)
Pancreas	3617 (6.23)	6124 (10.55)	1563 (3.17)		22	9	8 (6-11)
Larynx	4128 (7.11)	2428 (4.18)	1227 (2.49)		84	60	52 (47-57)
Lung	21,724 (37.44)	22, 691 (39.11)	8907 (18.05)		42	18	14 (12-15)
Uterus : cervix	4172 (7.19)	1811 (3.12)	742 (1.50)		87	69	64 (60-68)
Uterus : Endometrium	4717 (8.13)	1210 (2.09)	239 (0.48)		90	78	75 (71-79)
Prostate	19,772 (34.08)	8926 (15,38)	668 (1,35)		88	70	62 (58-65)
Bladder	10.187 (17.56)	4208 (7.25)	742 (1.50)		82	65	61 (56-65)
Brain, CNC	3072 (5.29)	2621 (4.52)	1362 (2.76)		49	26	21 (16-27)
All cancers except skin	217, 459 (374.80)	137, 322 (236.68)	42, 351 (85.84)		70	52	47 (46-48)

The rates and incidences are expressed for 100,000
CI: confidence interval

Table II-2: cancer in France (source: EUCAN 1999). Whole population (men and women)

Relative survival takes into account the expected survival of the whole population and the risk of death by causes other than cancer. For example, it was obtained for the population studied using the ratio: survival observed at five years for subjects in the population who had the cancer since being studied divided by the expected survival at five years for the whole population studied.

Early deaths correspond to deaths from cancer before 65 years of age.

II.5.4.2 Estimates of the target populations for carbon ions

The incidence data was taken from data in the French cancer registers for common tumours. The incidence data for rare tumours was taken from data in the European and American literature. The numerical data obtained from the incidences is given only for the French population. The potential recruitment could be much wider if countries bordering on France which do not have carbon ion hadrontherapy facilities were included.

The fraction of patients for whom treatment with carbon ions could be beneficial in comparison with the best current treatments has been estimated for each location, in order to fulfil the selection criteria defined in section II.4.5.2.These estimates are based on an analysis of the medical literature and on data published by a European project (EULIMA European project; German project and Italian project) [65] [66] [67] [68] [69] [70] [71]. The actual recruitment of patients will depend on their distance from the treatment facility, as indicated later.

A medical research project common to all the European hadrontherapy centres and also the Japanese centre should specify the research priorities and methods.

• Rare tumours

Most rare tumours can only be treated with carbon ions, which represent a radiobiological and ballistic advantage in comparison to X photons.

Melanomas of the choroid are currently being successfully treated in France at the Orsay and Nice protontheraphy centres (and to a lesser degree by brachytherapy) and therefore are not included here.

Tumour	Incidence /100 000	Number	% for ions C (estimate)	Target population (estimate)
Skull base, spinal and paraspinal tumours				
• chordome, chondrosarcome	0.1	60	100	60
• meningiomas	0.3	180	50	90
•divers	0.5	300	50	150
Soft tissue sarcomas (excluding limbs)	0.8	480	60	290
Salivary glands	0.6	360	30	100
Low grade gliomas	0.85	500	50	250
Anaplasic cancers of the thyroid	0.75	450	50	225
Facial sinus tumour	1.2	720	50	360
Pituitary gland tumours	0.3[2]	180	20	35
Paediatric cancers	3.52	300	20	60
Local recurrence after photons	> 0.5	> 300	100	300
(choroidal melanomas)[1]	0.7	400	-	-
Total		*> 4 400*		*1 945*

[1]Elective protontherapy indications (or brachytherapy)

[2]For 100 000 children

Table II-3: estimate of the target populations of potential indications for carbon ions (rare tumours)

• Common tumours

For common tumours carbon ions offer a radiobiological and/or ballistic advantage compared with photons. Certain tumours can only be treated with carbon ions, while others could receive a combination of photons and carbon ions.

Tumour	Incidence /100 000	Number	% for C ions (estimate)	Target population (estimate)
Liver	7.3	4200	15	630
Digestive cancers (pancreas, bile ducts)	13	7800	25	1450
Lung	37	22, 000	15	3300
Oral cavity - oropharynx	23	13, 000	20	2600
Uterus- (cervix, endometrium)	15	9000	15	1350
Rectum	11	6600	15	990
Bladder	17.5	10, 000	15	1500
Brain, Central Nervous System	5.3	3000	15	450
Cavum	0.45	280	30	84
Prostate	34	20, 000	20	4000
Total		*88, 080*		*16, 354*

Table II-4: estimate of the target populations of potential indications for carbon ions (common tumours)

II-6
Non cancerous indications

The objective of functional neurosurgery is to modify the operation of the neuronal circuits in three pathological situations:

• neurogenic pain or central pain connected with a malfunction of the pathways and circuits for transmission of pain impulses

• focal epilepsy, resistant to pharmacological treatments, connected with abnormal hypersynchronous discharges affecting part of the cerebral cortex

• parkinson's disease which is a motor programming disorder with respect to a degeneration of the dopaminergic cells of the substantia nigra of the brain stem.

To date the methods used in the context of functional neurosurgery are represented by:

• Cortical ablation surgery in epilepsy

• Creation of focal lesions of small volume targets using stereotactic electrocoagulation via intra-cerebrally implanted electrodes

• The chronic neurostimulation of the target structures by implanted electrodes which is successfully used in Parkinson's disease and central pain, and which is currently being evaluated in certain forms of focal epilepsy

The required precision of the lesions which can be achieved using ionic irradiation (two millimetres) leads to the hope that neurosurgery may use a hadrontherapy approach for certain indications. This could, in particular, replace approaches using focal electro- or thermo-coagulation and could also be used to replace conventional cortical ablation surgery (cortectomy) in epilepsy.

The possibility of delivering a high level of energy, voxel by voxel, and achieving precise anatomical contouring of targets is one of the major advantages of hadrontherapy.

II-7
Treatment network and clinical research

II-7-1 Coordination of treatment and clinical research. Recruitment of patients

II.7.1.1 European network

Coordination of light ion hadrontherapy at a European level (ENLIGHT)[5] has been initiated by the European Society for Therapeutic Radiology and Oncology (ESTRO). This collaboration will cover clinical research (epidemiology and selection of patients, clinical trials). The European dimension will be essential for phase II and, more so for, phase III clinical trials.

[5]The ENLIGHT network (European Network for Light Ions Therapy) was created in 2001. It brings together five European projects (Heidelberg/Darmstadt, Milan, Stockholm, Vienne and Lyon) and CERN. There will be working groups on: radiobiology, clinical, technological and economic aspects.

II.7.1.2 Radiotherapy network

Around half of the patients will receive irradiation by carbon ions only. They will be **managed entirely** by the medical team of the hadrontherapy centre. The management of other patients, who will receive radiotherapy, partly using photons and partly using carbon ions, will be managed in collaboration with the team referring the patient.

It is not intended that the hadrontherapy centre should provide photontherapy. This must be carried out in a accredited radiotherapy hospital (predefined quality controls required) and the treatment plan drawn up jointly, to take account of the requirements linked with both photontherapy and hadrontherapy. The establishment and/or use of local, regional and national networks (e.g. French National Hadrontherapy Organization, French Society of Oncological Radiotherapy, French National Federation of Comprehensive Cancer Centres for the Fight Against Cancer), and even European networks, must ensure optimal coordination of treatment and also provide targeted recruitment for the hadrontherapy centre. It is clear that the collaborative organisation of patient recruitment will be a key point in the success of the Centre.

II.7.1.3 Network of organ specialists

Diagnosis and treatment, at least initially, is usually carried out by organ specialists (neurologists, pneumologists, surgeons, etc). They will be involved in the establishment of this medical project at a regional and national level (in particular via their professional organisations). This collaboration must also enable optimal coordination of treatment and recruitment of patients for treatment with carbon ions. The importance of this collaboration and of patient recruitment must be stressed.

II.7.1.4 Patient recruitment

Using the network methods described above, the planned recruitment of patients can be estimated as follows, in terms of geographical origin:

For the urban area of Lyon, the total target population for carbon ions is estimated to be 700 patients a year. Assuming that 50% of these patients can receive carbon ion irradiation, this would represent around 350 patients. This estimate will, of course, require full cooperation between the city's three large medical sectors: HCL, CLB and private clinics.

Rhône-Alpes region: outside Lyon the target population is estimated to be 1100 patients a year. Bearing in mind the distances involved, it may be estimated that 20% of these patients could receive carbon ion treatment, that is, 220 patients a year.

France: outside the Rhône-Alpes region, the target population is estimated to be 16,000 patients a year. Here too, due to the distances involved and possible difficulties with cooperation, it may be estimated that 5% of these patients could be treated with carbon ion beams at the Lyon site. This represents a total, for the rest of France, of 900 patients a year. Provision must be made for the travel and accommodation of these patients. Such cooperation at a national level demonstrates that it is essential that this project is designed as a national project bringing together all the strengths of French radiotherapy.

International cooperation: cooperation with neighbouring countries, Switzerland and Spain (possibly even Italy, although there is a project for a centre in Milan) is expected. Contact has been made with radiotherapists and oncologists in Geneva and Turin, who should, a priori, agree to collaborate with this project. A maximum of 200 patients from other countries could be expected.

II-7-2 Clinical research

Clinical research is an essential part of the project. It is based on the performance of clinical trials, defined for each type of cancer. Three types of medical evaluation can be identified:

- Phase I trials

These involve a limited number of patients and are used to define the optimal irradiation dose and fractionation. Some of these trials have already been carried out at the NIRS, making it possible to move on to phase II, and even phase III trials.

- Phase II trials

These consist of treating a limited number of patients in the same way in a clearly defined clinical situation, in order to establish precisely the efficacy and the secondary effects of the treatment. These trials have been carried out for certain cancers at the NIRS and GSI (cancers of the lung, cancers of the skull base, hepatocarcinomas, etc).

- Phase III trials

These consist of comparing the best known and validated treatment with the "therapeutic innovation" (carbon ions), in order to scientifically evaluate the therapeutic benefit, and to define the exact advantages of carbon ion hadrontherapy in the arsenal of cancer therapies.

The methods used for clinical research must be specified in each situation under consideration.

II-8
Research and development in radiobiology

The application and optimisation of treatment using carbon ions requires progress to be made in the radiobiology of these particles. Only some of the questions have been answered and several areas still remain to be investigated. Amongst these the complete modelling of the RBE depending on the tissue and the acute and delayed effects is necessary for dosimetric prescription and planning. Another strategic area for the operation of the centre and the potential number of patients which could be managed annually, is the study of the optimisation of the number of irradiation sessions per patient (fractionation). One of the particularly original features of light ions is the possibility of reducing the number of treatment sessions while retaining the same levels of efficacy and tolerance. The study of this aspect is complex, and necessarily starts with the use of animal models, followed by phase I and II clinical trials.

The radiobiological problems which are raised by this therapeutic method are therefore located at different stages in the development of the project, which leads us to divide them into three types of objective in accordance with the stage of progress of the ETOILE project.

II-8-1 Preliminary objectives

The evaluation of the risks of stochastic effects in the radiological protection of patients is the main preliminary objective. Carbon ion hadrontherapy must provide a curative benefit for tumours which are currently radioresistant. This benefit in long-term survival must, therefore, lead to an evaluation of the risk of radiocarcinogenesis which could be associated with this type of treatment.

The body of data from the Berkeley experiment on more than 1000 patients does not show any increase in secondary cancers. However, a study specific to carbon ions tailored to the conditions of use planned for this project is to be carried out. It is based on two sources of information:

- Analysis of the group of patients from Berkeley and possibly those from Chiba and Darmstadt.
- A semi-theoretical study which is to be carried out using the methodology employed by the proton-therapy team at the Paul Scherrer Institute (Switzerland) to evaluate this risk for protons.

It should be noted that for proton treatment and photon treatment of the same pathology, the carcinogenic risk of protons is lower than that of the conventional photon treatment. This is essentially due to the reduction of the volumes of healthy tissue irradiated as a result of the better ballistics of protons. It is not possible to simply extrapolate these results for carbon ions, due to their RBE characteristics, and a specific study will be necessary. This will be carried out in 2002-2003, coordinated by the radiological physics team of the Grenoble University Hospital and the postgraduate medical physics research program staff at Toulouse, in the setting of a university thesis.

II-8-2 Objectives of the technical development of the project

• Describe and model the structure of the deposition of energy from carbon ions in living matter.

• Investigate the nature and repair process of radiological lesions caused by a beam of carbon ions with different LETs.

• Investigate radiobiological modelling of the RBE to be adapted for planned biological dosimetry.

These three objectives are complementary. They should contribute to improving the definition of the biophysical and radiobiological parameters which will be used to model the biological dose to be delivered to different irradiated tissues. They are not, however, preliminary objectives which will lead to other stages, since the GSI model developed by Kraft has been validated and is adequate to enable correct planning of carbon ion treatments. However the pragmatic GSI model is not unanimously accepted and it does not include current data on the structure of the deposition of energy in matter and it is not universal. In particular, its applicability if the type of ion is changed has not been proven. There is, therefore, a large area of pre-clinical radiobiology which can benefit from the ETOILE project for its development. This will lead to optimisations at the time of the transfer to clinical activity.

The experimental part of this work must make use of ion beams available elsewhere, GANIL, GSI, etc. These fundamental radiobiological research objectives have been presented to a group of radiobiology research scientists.

This ad hoc group of research scientists, all located outside the Rhone-Alpes region in different institutions (CEA, CNRS, University Paris-Sud, Nice,

Toronto) could be coordinated and strengthened by a collaboration with the mixed radiobiology team at the University of Grenoble1/INSERM. This team is planned to be established in 2002-2003 as part of the Institute of Neuroscience project at Grenoble, and as part of its research projects could collaborate with the radiobiology activities devoted to the ETOILE project at Lyon.

Research and development in radiobiology is one of the areas for European cooperation within the ENLIGHT network.

II-8-3 Long term objectives for the operational clinical period

• To study the effect of fractionation of the treatment on animal tissue models, and then in therapeutic trials.

• To evaluate predictive factors and eligibility criteria for carbon ion treatment, particularly the diagnostic methodology for tumoural hypoxia.

• To assess the chemo-hadrontherapy combination treatment.

Investigation of the reduction of the fractionation, both in animal experiments and clinically has already started at the NIRS. The scope of this area of research in the ETOILE project will depend on the state of progress and the clinical and biological problems which remain to be investigated. It will, however, be a crucial area, since the shorter the length of treatments, the greater the number of patients who can be treated, with the same number of treatment rooms. This will require an increase in the planning capabilities, which essentially means an increase in human capacity.

The experience acquired from the patients treated according to the recruitment and selection criteria described earlier, will lead to a critical analysis of the successes and failures of the treatments. A predictive (biological and oxymetric characteristics of the tumours, etc) and retrospective procedure must be set up to refine the indication and prognosis criteria for carbon ion treatments. Proteomics and genomics will have an important role in this evaluation procedure. These techniques are currently developing rapidly in oncology and will make full use of the progress made by the time the first patients are recruited for hadrontherapy treatment.

The generalisation of chemo-radiotherapy combinations in "standard" protontherapy was one of the main areas of progress in radiotherapy in the 1990s. Today, this procedure is gradually being applied with the more advanced forms of radiotherapy such as hyperfractionated treatments, and tomorrow, will also be possibly applied with hyperselective treatments such as micro-beam radiotherapy. The desire to optimise hadrontherapy will certainly lead to the assessment of chemo-radiotherapy combinations. Studies in this area are already under way, with the experimental radiotherapy developed at the European Synchrotron at Grenoble (ESRF) by the Synchrotron Radiation and Medical Research team. This field of research will be stimulated considerably by the development of the first carbon ion treatments and will be investigated in the medium- and long- term mainly with regional teams.

II-9
Technological research and development

Research and development could involve a number of fields. Projects which will be defined later will be designed around the necessary adaptation and improvement of the tools used by medical doctors, radiological physicists, operators and nurses for carrying out day-to-day treatments. They will concern initially software for imaging, planimetry, and control of the positioning and internal movements of the patient. They will all, if possible, be carried out at a European collaborative level, with the other existing projects (Germany, Sweden, Italy and Austria). This partnership with be facilitated by the creation of the ENLIGHT subject-based network. The first meeting took place at CERN in February 2002.

Other areas of technological research and development could arise during the design and development of the ETOILE project. Thus technological advances concerning active beam control, spill quality or aspects connected with the positioning of the patient and on-line dosimetric monitoring will be evaluated and possibly developed within the ETOILE project.

This research and development will lead to the development and improvement of high-performance tools, designed not only for the European centres offering carbon ion radiotherapy, but also centres providing proton and neutron treatment. In addition many conventional radiotherapy centres will benefit from these innovations.

Four technological research and development projects are presented below with a summary of their objectives. Introductory sheets on each project are given in the appendices.

II-9-1 Physical interactions between light ions and living matter

1. To extend the codes for calculating the tracks and the penetration of light ions in the specific cases of very high depositions of energy (Bragg peak) in living matter
2. To assess nuclear effects during the penetration of ions: associated positron fragmentation and emission
- modelling of the spatial distribution for each isotope produced
- experimentation on water phantoms and small animals, with the GANIL beam, using the micro-PET scan prototype developed by the Crystal Clear group, Lyon
3. To model the dose deposited by all the ions using the reconstructed PET image

II-9-2 Treatment planimetry

1. To use the existing system, in order to develop, adapt or improve planimetry software for photons, protons and carbon ions which can be used, distributed and interfaced with the software used in conventional radiotherapy
2. To improve this software by the integration of:
- extended merging of imaging methods
- nuclear fragmentation
- biological effects (RBE)
3. To improve this software by incorporating organ movements

II-9-3 Positioning and control of the ballistics

1. To develop high-performance tools for the alignment and merging of multimodal images (functional and anatomical) for the preparation and control of treatment. Two types of algorithm will be developed:
- real-time for control during treatment
- deferred time control for analysis and diagnosis before and after treatment sessions
2. To construct tools to help with assisted segmentation of volumes to help the doctor in the task of contouring
3. To develop tools to assist with initial positioning and monitoring of movements. This will require two levels of study:
- control of the position of the patient in relation to the system (development)
- control of the position of the organs in relation to the patient (research)

II-9-4 On-line PET imaging

1. To simulate the fragmentation phenomena and the PET images by such a system
2. To adapt the new technologies developed for the new generation of micro-PET scans
3. To carry out experiments on phantoms and on animals
4. To design and build a prototype

This project could also lead to the development and creation of an "advanced whole body PET" camera for use in the early detection and metabolic monitoring of tumours.

II-10
Health economics research and studies

The French carbon ion hadrontherapy project falls within the framework of therapeutic innovations. As with the other Europeans projects, sufficient clinical data to define this treatment as a therapeutic standard will only be collected once the first centres and coordinated clinical trials have been completed. This simplified preliminary design document provides most of the information necessary to make an informed decision.

This project offers a unique opportunity for a prospective medico-economic evaluation, taking into account the expected benefits and the costs, with an approach comparing therapeutic alternatives, and an analysis of the decision-making process concerning a significant therapeutic innovation. This research is to be carried out in the context of a scientific thesis at the Health Systems Analysis Laboratory (Laboratoire d'Analyse des Systems de Santé, LASS), UMR CNRS/Université Claude Bernard Lyon 1.

The objectives of this research are:

To estimate, for the main indications proposed, the annual number of new cases eligible for carbon ion hadrontherapy: epidemiological data

The epidemiological data which is currently available is not sufficiently complete to be able to specify the number of patients who may benefit from carbon ion hadrontherapy for each indication proposed. A evaluation will be carried out using records of tumours, on the Permanent Cancer Enquiry ("Enquête Permanente Cancer") database of the National Federation of Cancer Centres (Fédération Nationale des Centres de Lutte Contre le Cancer), and using a one-off national survey. This study will make it possible to define the priority indications, according to the limits of patient recruitment, and the level of expected benefit (cf. below).

To investigate the trajectories of patients - medico-economic evaluation

The accurate evaluation of a new therapeutic method at a medico-economic level, requires taking into account the whole of the therapeutic treatment, diagnostic situation, and the alternative therapies and combined therapies, monitoring and subsequent treatment of complications, and possible progression or recurrence (often connected with the choice of therapy). The local control rates published in the literature are major clinical elements justifying the current European projects. For each of the therapeutic options, the efficacy, toxicity and quality of life, can be estimated from the data in the literature, in the form of "probabilities". These can then be used for modelling the options of initial therapeutic trajectories (carbon ions or existing standard treatment) in the form of a decision tree.

The costs of the different therapeutic strategies ("trajectories") for each type of indication will be estimated, so as to provide cost/benefit data. This model will make it possible to test different hypotheses of therapeutic advantages with hadrontherapy and the expected consequences in medico-economic terms. This methodology and its limits will be defined.

Health-based decision: therapeutic innovations

Therapeutic innovations pose the problem of funding their medical and medico-economic validation, in particular when a large capital expenditure must be made, as is the case in the European carbon ion hadrontherapy projects.

Health-based decisions, particularly in the field of therapeutic innovations in oncology, will be analysed. The medical and medico-economic evaluation methods and methods for making decisions regarding funding by the community are different depending on whether drugs developed by the pharmaceutical industry or diagnostic and therapeutic technologies (in particular radiotherapy) are involved. The selection criteria chosen will be examined in medico-economic terms, as well as the consequences of whether or not the innovation is extended into general use.

The contribution of a number of economic theories for decision-making in health will be examined in the context of the hadrontherapy project.

Hadrontherapy in France

There are currently three hadrontherapy centres in France: the Hôpital de la Source at Orléans (neutrons), the Centre de Protonthérapie d'Orsay (protons) and the Nice cancer Centre, MEDICYC (protons, and possibility of neutrons). This project for the creation of a Centre at Lyon in the Rhône-Alpes region will be the fourth.

The legal structures, very different for each centre, and the present funding methods will be analysed so that they can be used as a basis for the proposals to be made for the carbon ion hadrontherapy centre.

The development of hadrontherapy in France was the subject of a medico-economic evaluation carried out by the National Agency for the Development of Medical Evaluation (Agence Nationale pour le Developpement de l'Evaluation Médicale, ANDEM) in 1995: "therapeutic use of cyclotrons in oncology: clinical and economic evaluation". The present French project must be used as an opportunity to update the data and propose new recommendations validated in particular by the National Agency for Health Accreditation and Evaluation (Agence Nationale pour l'Accréditation et l'Evaluation en Santé, ANAES, which has replaced ANDEM). This analysis must be the basis of a common medical project for the development of hadrontherapy in France.

II-11
Training of radiological physicists

The ETOILE project will require a large number of medical physicists, both in its development phase and in its future operational phase. It is clear that France has urgent needs, in terms of personnel, at the scientific and university level, of this body of specialists whose skills and dedication are unanimously recognised by the teams of radiotherapists. The shortage of medical physicists - like the shortage of radiotherapists - is already hindering the modernisation of French radiotherapy.

There are plans to create new career paths for radiological physicists in the context of the ETOILE project, with their dual skills in Sciences/Health. The universities of Grenoble and Lyon (UJF and UCBL) are currently working together to develop advanced training courses, which could start in 2003.

France is also suffering from a shortage of doctor/radiotherapists. This question is more complex and will not be examined here. It has already been mentioned in the context of the ETOILE project.

• III•

Functional specifications for a treatment centre

III-1
Medical functional specifications

The functional specifications have been drawn up by oncologist/radiotherapists in collaboration with medical physicists, physicists and specialists in accelerators.

Various aspects have been taken into account, in particular the need to:
• treat deep-seated tumours
• optimise the machine for carbon ions, with the possibility of accelerating other types of ions
• obtain a deposition of the dose in the target volume which is as uniform as possible
• adjust the point of impact of the beam in as precise and reproducible manner as possible
• measure the doses deposited both on-line and in other ways
• provide conformal irradiation with a guaranteed quality and continuity

Machine functionalities

- **Choice of ions**

The study will be carried out for carbon ions. The possibility of accelerating other ions, from protons to oxygen, will be taken into account in the definition of the characteristics of the machine and in the aspects linked to radiation protection. This wide range of ions would enable results of irradiation obtained with each type in the same centre to be compared.

- **Characteristics of the beams**

In order to be able to treat all types of tumours, a maximum depth of 27 cm had been selected. The minimum depth required has been set at 2 cm. The maximum size of the required field of irradiation is 20 x 20 cm^2 (the field of irradiation corresponds to a section of the target volume).
The target volume must be precisely irradiated in all three dimensions. The lateral penumbra, defined between 80% and 20% of the prescribed dose must be less than 2 mm more than the penumbra due to diffusion in the tissue. The distal drop in depth, defined between 100% and 30%, must be less than 3 mm. Finally, the direction of the incident beam must be well known so that the impact of the beam has a lateral precision better than 2 mm.

- **Beam scanning system**

In order to obtain consistent and precise irradiation, an active rasterscanning system is envisaged for the beam. Active rasterscanning consists of delivering doses in small volumes (voxels) predefined by the treatment plan. This irradiation is carried out slice by slice in the target volume corresponding to a determined energy of the beam coming from the accelerator. The beam is moved laterally in both transverse directions while its direction, shape and intensity is checked every 20 to 30 microseconds.

However, to be able to deal with targets the position of which can vary over time (according to the respiratory or cardiac rate), the possibility of having a passive system (instead of the active system) must be included. The passive system could consist of inserting a diffusion device (variable thickness mechanical moderator) a compensator and a number of collimators in the final path of the fixed energy beam, to obtain a uniform distribution of the doses in the whole target volume.

- **Dose rate**

In conventional radiotherapy the distributed dose is expressed in Gray (Gy)[6]. A physical dose of 2 Gy is commonly delivered per beam direction and per session. In the case of carbon ion hadrontherapy, and taking into consideration the preliminary results, it is possible that the biological dose could be significantly increased. It would therefore be advisable to be able to deliver a physical dose of 2 Gy which could, therefore, be provided with a treatment time of one minute for a volume of one litre. This physical dose must be precisely defined, in particular when using a beam rasterscanning system where the dose delivered in small volumes must have a very high level of reproducibility. A precision of ± 2.5% is required over the whole of the target volume. The possibility of interrupting the irradiation during the scanning of a plane where sections of the tumour are not connected must be included.

[6] 1 Gray (Gy) corresponds to the dose absorbed by a 1 kilogram mass of material in which ionizing rays communicate on average an energy of 1 joule.

• Possibility of respiratory synchronization

The respiratory movements cause movement of the intra-thoracic and intra-abdominal organs. To take account of these movements on the target volume inside the patient, a system for synchronising the irradiation (active or passive) with the respiratory cycle ("gating" loop) must be included.

• Beam incidence

In conventional radiotherapy several incidences of the incoming beam (generally 2 to 5) are used. This is possible due to the isocentric rotation of the linear accelerators which are used. The hadrontherapy centre must provide the possibility of using fixed beams (horizontal or vertical) or mobile beams for which the incidence[7] can be varied (rotating isocentric gantry). If there is no gantry it must be possible to orientate the patient's support (bed or chair) through six axes.

• Reliability, flexibility

A number of ion sources will be provided, so that the ion accelerated can be changed in less than an hour. The type of source will be defined for its ability to maintain the required performance levels in terms of current and stability.

Since the "machine" must be a medical machine which is required to be safe and reliable, the technologies used must be well understood. The energies and intensities delivered will vary in times of around a second. It must be very suitable for accelerating high energy light ions. It must provide a precise active distribution of the dose in the target volume while varying the energy and intensity of the beam.

An average machine availability of 97% will be required over the year. The average time to repair a first level fault must be no more than 1 hour.

Immobilizing the patient

As with conventional radiotherapy, the immobilisation devices will be the most modern and those providing the highest performance. They will be constructed on site and the centre will be involved in their development. They will be fixed to the patient support in order to obtain maximum precision in the fixed system of reference of the room.

[7] This study appeared to be necessary during the redaction of the technical project report.

Treatment planning system

The planning of the treatment is based on the principles of simulation. The patient is placed under the same conditions as those of the treatment (same immobilisation device and positioning on bed or chair). An image of the region to be treated is obtained using the latest generation CT scan to achieve the best possible precision, and with the additional help of a Magnetic Resonance Imaging (MRI) system. A simulation room is, therefore, required and this must be equipped with a reference system and a patient support device identical to those in the treatment rooms. It must also have a CT scan and optionally a MRI system.

The virtual simulation and the dosimetry will be carried out using high performance graphic workstations and using specialised networked software (e.g. Dr. View from HIMAC or Voxelplan from GSI).

Patient positioning. Quality control.

In order for the dose to be accurately deposited in the target volume, the volume must be perfectly positioned in relation to the reference system of the treatment room and the axis of the beam. This 3-D reference system can be displayed using laser beams in the treatment room or defined using stereotactic frames. It must be possible to check the reliability of this reference system regularly in relation to the room and the beam.

• Mobility of the patient support

The patient will be placed on a "cradle" bed or a treatment chair. It must be possible to incline this device by ± 30°. The bed and the chair must be movable and remotely controlled in three dimensions with millimetre precision. This movement could be controlled from a console located in the irradiation room or from outside from the irradiation control room.

• Checking positioning

At each treatment session, the patient is repositioned with his personalised immobilisation system. The patient's position is then checked by X-ray, and if necessary with the respiratory synchronisation system. The operator then measures the difference in

position between this image and the reference image obtained during the simulation. If the difference is greater than 1 mm, the operator controls the movement of the bed with millimetre accuracy to correct this difference.

- **Check using X-ray imaging**

The position of the patient or preferably that of the target volume, is checked using three X-ray tubes (generally in the ceiling) and three detectors placed according to the three spatial axes. These radiography systems must be movable and it must be possible to move them to any position around the examination bed or chair.

The checks concerning the patient (imaging, position, movement) will be carried out in the pre-positioning room.

Verification of the dose deposited (dosimetric control)

Controls of the intensity, direction and shape of the beam must be carried out extremely quickly (a few tenths of a microsecond) and duplicated using appropriate devices such as ionization chambers. These irradiation checks must be independent of the checks on the accelerator beam and its routing to the treatment rooms. The beam energy should be known very precisely.

The presence of ^{11}C and ^{10}C (ß+ emitters) resulting from the fragmentation of some of the incident ^{12}C ions will enable, using an appropriate PET camera, in situ spatial and dosimetric checking of the irradiation and verification that the dose delivered complies with the prescribed dose. This camera may be located in the treatment room (as at GSI) or outside. Recent developments in the field of scintillating crystals should make it possible to envisage the on-line use of such a camera to obtain images of the beam path (and probably the dose deposited), which are sufficiently bright, with a time of around one second.

Radiological protection

The radiation protection to be installed at the facility is aimed at protecting workers and patients as well as the environment. Access control systems and systems for measuring the radiation in the treatment rooms and machine rooms, and systems to stop the beam in the event of an anomaly, must provide all the safeguards and the redundancy required for safety.

Control system

The controls concerning the accelerator beam (energy, intensity, spatial distribution, uniformity, profile, emergency stop) and the control of access to the machine rooms and treatment rooms (radiation measurements, beam closing down) must be centralised in a machine control room which is separate from the irradiation control rooms.

The irradiation must be controlled from a console located close to the treatment room and the pre-positioning room. This console will be used for storage of the irradiation parameters and all the parameters connected with the machine will be fed back to this console. Specialist software will be used to control the irradiation taking into account the parameters of the treatment plan, the machine beam, the general safety devices, the positioning of the patient and the clearing of the room.

Quality assurance, tests

Daily, monthly and annual checks on the equipment and the functionalities must be defined for both the irradiation, the machine and the radiation monitoring.

Rooms

The hadrontherapy centre will have three treatment rooms. Two will be equipped with fixed horizontal beams and one with a fixed vertical beam. A request has been made to examine the possibility of installing a device (gantry) for rotating the beam 360 degrees, instead of the vertical beam, in order to obtain different angles of incidence on the patient. Time will be reserved for radiobiology research programs and for the development of these treatments.

The treatment rooms will be equipped identically with:
- a beam conformation system
- a dosimetric system for quality control
- a patient support positioning system

The possibility of adding further diagnostic, imaging or position verification equipment must be included.
Each treatment room will have an associated pre-positioning room.

The civil engineering design must include the possibility of the subsequent addition of a fixed horizontal beam in the vertical beam room if the solution with a gantry is not chosen.

Building

The building is to be located in a hospital environment. It will be designed in such a way that it can be extended so that additional facilities can be incorporated in the site. The surrounding area and the patient reception areas must be given particular attention. The technical areas connected with production, shaping and distribution of the beams must be kept separate from the medical areas. Each treatment room is to have an associated pre-positioning room and an irradiation control room. These rooms will be separate and will contain similar equipment.

The building must be designed to receive patients for all the steps prior to carbon ion treatment: medical consultations, treatment planning, immobilisation devices, imaging (CT scan, MRI system) as well as post-therapy follow-up.

In the event of young children being treated, a room for general anaesthetics must be provided, with a recovery room.

Site

The reference site will be chosen according to its proximity to hospitals and research laboratories and to its accessibility (airports, train stations, motorways) for the patients. Its surface area will be large enough for there to be space in reserve for any extension.

Special studies will be undertaken to determine the nature of the ground, the composition of the subsoil (in particular for civil engineering studies, water supplying for cooling the various devices), the electricity inlets, the population, the access routes and more generally everything relating to the environment.

Summary of the medical specifications

Projectiles	ions $^{12}C^{6+}$
Possibility of other projectiles	from protons to ^{16}O
Time for changeover between two types of particle	< 1 hour
Depth of penetration of ions (p, C)	2 à 27 cm in water
Maximum dimensions of the area of irradiation (perpendicular to the direction of the incident beam)	20 x 20 cm^2
Maximum continuous physical dose rate	2 Gy with a traitement time of one minute per litre
Distribution of the dose in the target volume cible (I and E)	
Distal drop 100% - 30%	less than 3 mm
Lateral penumbra 80% - 20%	less than 2 mm
Lateral precision of the direction of the incident beam	2 mm at the target volume
Diameter of the beam at mid-height	variable from 4 to 10 mm
Spatial resolution of the field of irradiation	~ 2 mm
Angular rasterscanning of the beam	Yes
Distance between scanning magnets and isocentre of the tumour	> 3 m
Possibility of distributing very low doses	Yes
Possibility of several incident directions of the beam in one room	Yes
Safety of the patient:	
- rapid shutting down time	200 ms
- uniformity of the dose in the target volume	tolerable deviation ± 2.5%
- precision of the dose delivered	± 2.5%
Irradiation techniques with the beam	
Active : energy can be varied rapidly	Yes
intensity can be varied rapidly	Yes
position of "pencil" beam can be varied	Yes
Examine the possibility of also having passive irradiation	Yes
Number of rooms [8]	- 2 treatment rooms with horizontal beam - 1 treatment room with vertical beam (with the possibility of installing an additional horizontal beam
Equipment in treatment rooms	- possibility of robot-controlled beds and/or chairs - 3 X-ray tubes for digital imaging, possibility of PET - marker systems
Rooms attached to each treatment room	1 pre-positioning room 1 irradiation control room
Number of simulation rooms with CT scan	1 to 2
Number of patients per annum	50 to 100 in the first year200 to 500 in the second year, 500 to 1000 in the third year
Minimum dosimetry (measurements) just before the patient	Ionisation chambers
Per beam line	- 2 for controlling the position and shape of the beam - 2 for controlling the dose - 1 for redundancy
Number of treatment planning rooms (planned dosimetry)	2 rooms with 3 consoles per room
Precision of the positioning of the patient in relation to the beam, with appropriate immobilisation device	Head: 1 mm Body: 2 mm
Areas to be provided	Reception, management, administration, secretarial offices, waiting rooms, consulting rooms, anaesthetic room, offices for: medical doctors, physicists, engineers, technical areas, maintenance, storage (including activated materials), diagnostics, library, archives, visitors, meeting, rooms, toilets
Assumption for work with three treatment rooms	1000 patients routinely treated per annum after three years' operation 15 sessions on average per patient 220 days of treatments per annum

Table III-1: summary of the medical specifications

[8] During this preliminary design the benfit of carrying out the preliminary investigation of a treatment room with rotating isocentric gantry has come to light.

III - 2
Technical specifications

Variable energy accelerator	Synchrotron
Sources	2 ion sources for carbon ions and protons (+ possibility of using other ions) ECRIS type (Electron Cyclotron Resonance Ion Source)
Ions delivered in the rooms	$^{12}C^{6+}$, $^{1}H^{1+}$
Final energies for 2 to 27 cm penetration in water	C : 85 – 400 MeV/uma p : 50 – 200 MeV
Variation of the energy and intensity	The variation of the energy requires rapid adjustments lthe accelerator (around 1 second)
Variation of the penetration depth	In 1 mm steps if the penetration is less than 20 cm In 1,5 steps if the penetration is greater than 20 cm
Variation of the beam size (total width at mid-height)	4 to 10 mm spot with diameter adjustable by steps of 2 mm at the patient
Number of energy steps	255
Typical beam intensity for a a physical dose rate of 2 Gy/min per litre	Maximum number of particles per spill at the patient: $^{12}C^{6+}$: ~ 4×10^{8} protons: ~ 1×10^{10} typical values for active scanning (ref : PIMMS [7] in volume II)
Variations for each energy according to the treatment plan and the shape of the tumour	Imax/min intensity variation = 1000 Cycle duration : 1 to 10 seconds
Fluctuation of the position of the	Less than ± 15 % of the diametre of the spot at mid-height
Rasterscanning of the beam in the treatment room	Horizontal and vertical scanning magnets
Parallax fault	Distance between scanning source and isocentre of the tumour greater than 3 m
Easily variable beam entry angles	Rotating isocentric gantry instead of the fixed vertical beam
Reproducibility of the dose delivered, its uniformity and its contours	Contamination of the beam less than 1% Precise on-line monitoring of the parameters of the beam On-line monitoring of the spectrum of the source ions
Fast stopping of the beam	Rapid deflector, in 200 µs Associated mechanical stopping of the beam

Table III-2: Summary of the technical specifications

• V •

V - 1
Treatment plan

V-1-1 Introduction

3-D conformal irradiation of tumours by ion beams consists of delivering the prescribed dose while conforming as closely as possible to the volume to be irradiated. This conformation may be carried out with an ion beam which is either actively or passively shaped. The choice and validation of the treatment technique requires calculation of the dose distribution on a treatment planning system involving the anatomical data on the patient and the characteristics of the beam.
The treatment planning system systems used with carbon ions in Germany (GSI) and with protons at the Orsay protontherapy centre (CPO) are described briefly here.

V-1-2 Experience at CPO-Orsay (France)

The CPO has a 70 or 200 MeV proton beam. To ensure coverage of the whole tumour, Orsay uses a passive system for shaping the beam. This technique enables an initial adaptation of the maximum path of the protons (linked to the energy) to the depth of the lesion to be irradiated, using a degrader and an energy modulator. A more precise adaptation is achieved with the creation of a customised compensator for each beam incidence. The lateral distribution of the protons must also be made uniform with diffusers for irradiation field dimensions encompassing all possible target volumes for a given clinical application. The conformation of the volume is achieved using customised collimators.

The treatment planimetry is carried out at CPO using IsiS software. This is a system used in conventional radiotherapy, at about sixty sites in France, and for which there is a proton module.

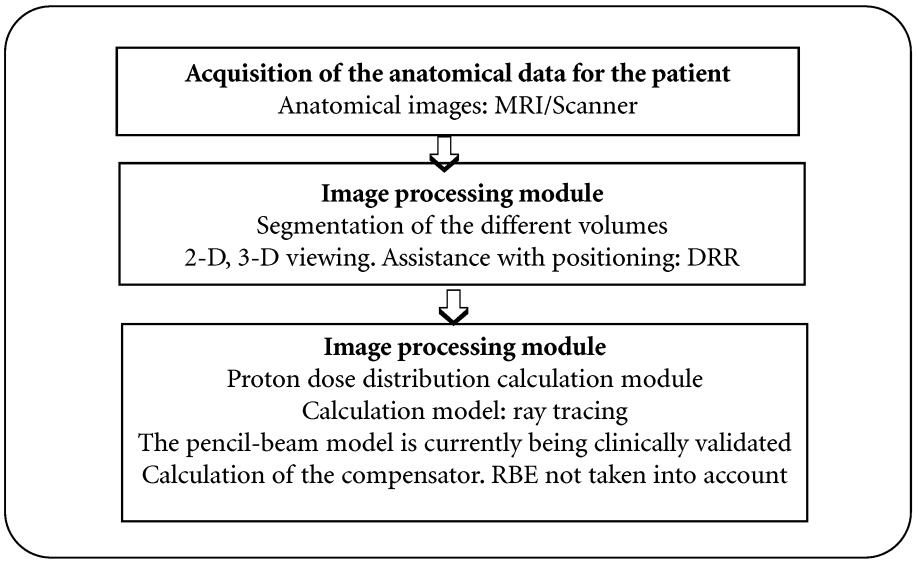


Figure V-1: diagram of ISiS software

With ISiS it is possible to use two sets of images simultaneously, which are aligned with one another, generally CT and MRI images. The images can be aligned outside ISiS (e.g. GE merge) or using ISiS.

The segmentation is carried out in 2-D, image by image, either in manual mode using a mouse by plotting continuous or discontinuous points, or in automatic mode by thresholding. The change to 3-D is made by interpolation. The DRR are calculated using a ray tracing algorithm. The model used clinically is the "ray tracing" model with special processing of the penumbra to take into account the enlargement in terms of depth, the air gap and the presence of the compensator {with the notion of a "theoretical" compensator (fine resolution) and "real" compensator (achieved with the machine tool)}.

With ISiS, CPO has a functional planimetry software. This system, developed at the Institut Curie, and distributed to a number of Paris hospitals enables an easy exchange of data for the planning of treatments for patients from a partner network. This system, widely used in conventional radiotherapy, benefits from developments in this field (pencil-beam algorithm [72], DRR, contouring assistance, etc).

V-1-3 Experience at GSI-Darmstadt (Germany)

With an active beam shaping system, 3-D conformal irradiation of tumours requires precise planning of the energy, position and intensity of the beam. Methods for optimising these parameters are complex and must take into account the specific physical and biological characteristics of the ions used [73].

At the GSI, an experimental model has been developed based on VOXELPLAN, the planimetry software used at the DKFZ in Heidelberg. This is a planimetry software for conventional radiotherapy which has a proton module and thus enables relatively flexible exchange of data with other dose distribution calculation codes. The calculation code developed at the GSI, TriP (Treatment planning for Particles), is a totally separate module which calculates the physical and biological dose distribution using VOXELPLAN data and which controls the beam.

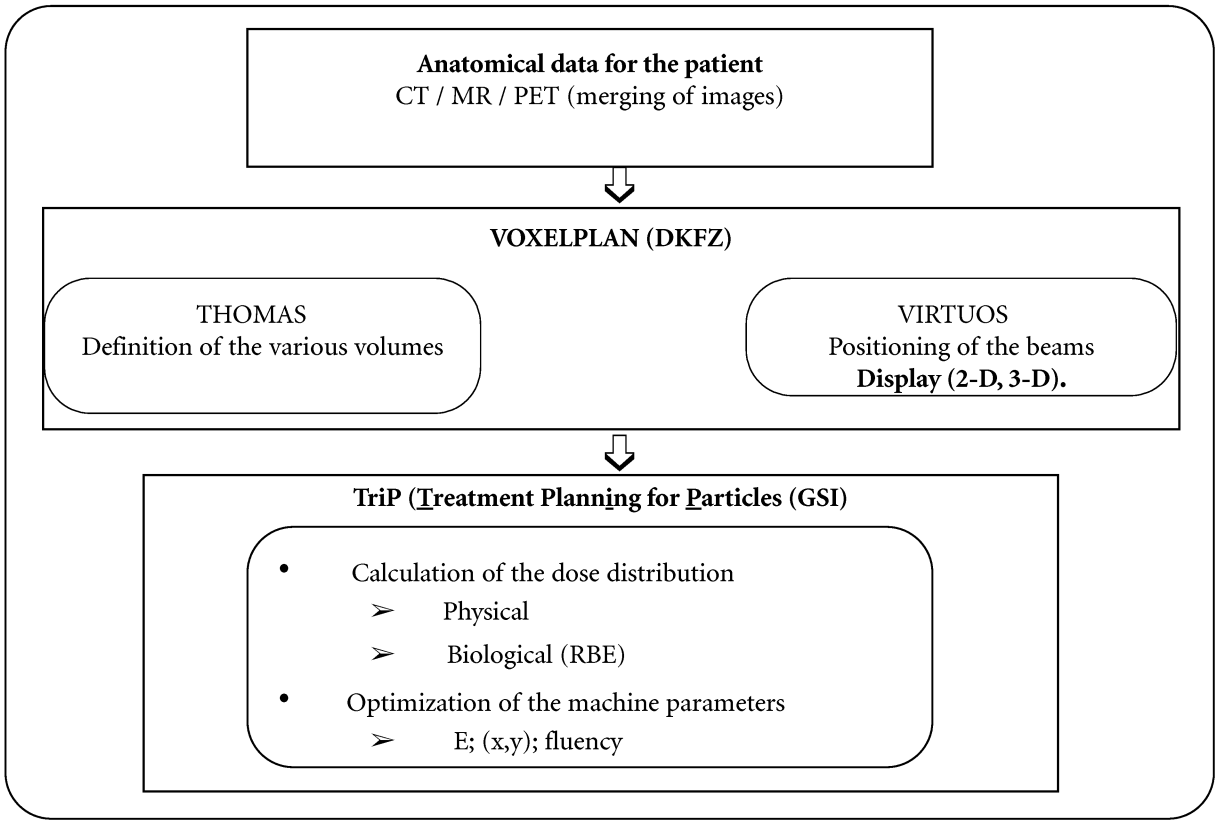


Figure V-2: diagram of VOXELPLAN and TriP sofwares

The anatomical data for the patient based on imaging is processed in the THOMAS module (Tools for The The anatomical data for the patient based on imaging is processed in the THOMAS module (Tools for Manual Segmentation). The VIRTUOS module (virtual radiotherapy simulation) is used to define the treatment plan and the dose requirements. TriP then works on the voxels generated by VOXELPLAN to calculate the physical or biological dose distribution and optimise the machine parameters.

GSI has chosen software used routinely for conventional dosimetry. VOXELPLAN can therefore be used for the entire definition of the planimetry of the treatment. GSI has developed its own TRiP code which uses the same data format as VOXELPLAN. This well studied choice ensures total flexibility of the system for calculating the final dose distribution with the possibility of taking into account the constant advances being made in radiobiology data. The software is also used to control the parameters of the ion beam (scanning, intensity, etc).

The Japanese at CHIBA also use experience acquired in protontherapy for which they have planimetry software based on the "pencil beam" algorithm. Research is currently being carried for the precise inclusion of fragmentation and RBE.

V-1-4 Specific characteristics of planimetry software for hadrontherapy.

"Imaging" module

With the most precise ballistics and the very large dose gradients offered by ion beams, it becomes necessary to carry out accurate contouring of the organs at risk and the target volume. To do this the system must allow the merging of images from all imaging methods at the disposal of the physician, so that the lesion can be defined precisely: anatomical images (CT, MRI, etc) and functional images (SPECT, PET, etc).

"Physical" module

The irradiation of living tissue by carbon ion beams involves complex phenomena which must be modelled accurately. It is necessary to take the phenomena of fragmentation into account:

• in the calculation of the final dose deposition, bearing in mind the fact that 12C ions will fragment
• for "online" display of the 11C produced, using a PET camera

The modelling of the biological effects of carbons on tissue is essential to achieve a biological radiation dose.

"Machine parameters and control" module

The treatment planimetry system must also enable definition of the characteristics of the beam to ensure conformal irradiation of the tumour.

For active beam control, the system must establish the energy "steps" necessary to cover the whole of the lesion. For each "step", i.e. each slice of the target volume, the system must also define the (x,y) scan of the spot (rasterscan).

Interface with other planimetry software

The system developed should have an interface for retrieving data for patients coming from other sites, which use different planimetry systems.

V-1-5 Strategic choices

A large number of planimetry systems are marketed in France for the photon beams found in conventional radiotherapy. Some of these systems already have or are developing models for dose calculation in protontherapy (ISIS, CADPLAN, CMS, etc). The advantage of these systems is that they are widely used and thus reliable and well known. The disadvantage is that, until now, they have not been very flexible and have only offered users a limited possibility of incorporating new modules or new data (RBE, etc).

There are a number of options. They must be evaluated and a strategy defined in consultation with the partners concerned. The industrial dimension must be taken into account.

Adoption of the German system (VOXELPLAN and TRiP)

This solution would enable us to have an operational system rapidly. The adaptation would consist of understanding the system developed at GSI and improving any weaknesses it may have. The disadvantage may be a lack of autonomy in relation to the research carried out at GSI.

To develop an interface between a system marketed in France and the TRiP module

This solution would provide a great deal of flexibility, allowing systems which are widely used in France to be used, which could be an advantage in the case of a network of partner centres. The manufacturers must, in this case, encourage data exchange systems.

To adapt software marketed for protons (for example ISIS) for carbon ion planimetry

The advantage of this solution would be the involvement, in France, of the team which has experience of proton planimetry that operates with passive beam shaping. It would have to be adapted for an active "rasterscanning" type system.

V-2
Carbon ion hadrontherapy imaging

Medical imaging brings together a number of techniques, tools and methods the objective of which is to display the anatomy and/or the operation of the human body in order to detect pathological variations. The main aim of these non-invasive techniques is either to provide assistance with diagnosis or to serve as an anatomical reference to the radiotherapist or as an anatomo-functional reference to the surgeon.

V-2-1 Diagnostic imaging

Apart from ultrasound, all imaging systems are currently based on three main techniques and physical principles.

CT scan (Computed Tomography)

Using radiological techniques based on the use of X-rays, anatomical information with very high spatial resolution and good tissue differentiation can be obtained with the CT scan. The CT scan is still the most precise and most widely used imaging technique due to its very fast and with very easy access. With a particularly high performance for the detection of cancers in the thoracic or abdominal regions, this technique, that gives access to the electronic density of tissues, is still the anatomical reference for planning radiotherapeutic treatments.

Magnetic Resonance Imaging (MRI)

More recently, MRI has enabled us to obtain not only very high resolution anatomical images with excellent contrast, but also functional and metabolic images. Thus, MRI constitutes the reference technique in particular for the study of cerebral pathologies due to its better pathological characterisation. As well as the perfusion and diffusion methods which will soon have an impact in the characterisation of the pathologies of tumours, "functional" MRI can be used for indirect monitoring of the metabolic and haemodynamic phenomena following neural activation. This technique is particularly useful in neurosurgery for the location of functional areas (language, memory) close to the tumour to be resected or treated, in the context of a pre-surgical or pre-radiotherapy report.

As for spectroscopy or metabolic MRI, this is a unique non-irradiating method for tissue characterisation. Through the detection of certain metabolites such as lactate, the marker of anaerobic metabolism, or choline, the marker of a characteristic membrane activity of tumour processes, spectroscopy can be used to identify certain tumours and particularly to characterise the regional metabolic variations which constitute an indicator of tumour activity. This approach thus enables the radiotherapist to define the target volume with greater precision and specificity.

Positron Emission Tomography (PET)

PET is an imaging technique which consists of detecting g annihilation photons produced coincidentally during β^+ disintegration in matter. Based on the injection of a molecule, which is the tracer of a metabolism or a function, associated with a positron emitting isotope, PET using ^{18}Fluoro-deoxyglucose (FDG) is used to detect the smallest tumours due to the increase in their glycolysis. Recent use of this technique for whole body scanning makes it an excellent diagnostic technique for oncological pathologies.

V-2-2 Place of imaging in the planning of treatment

In radiotherapy, the CT scan is the reference technique for detecting and delimiting the target area, based on which the dosimetric planning calculations will be made. However, in the context of new conformal radiotherapy or hadrontherapy techniques which have a much better ballistic precision, it seems necessary to define the target volume more precisely using anatomo-functional imaging.

In addition to the CT scan which is an excellent anatomical reference, it is therefore desirable to use MRI which gives a better tissue contrast in particular for cerebral imaging. Moreover, MRI can provide other information, either of a metabolic type with spectroscopy, or of a functional type with perfusion or activation MRI which provide better characterisation of highly heterogeneous tumour areas. Finally,

due to its excellent sensitivity and specificity, PET using FDG or methionine, is the best method for early detection of primary and secondary tumours. This technique will continue to be improved.

These different types of image, obtained using different methods, provide additional functional and anatomical information which are of great benefit for characterising the tumour area and thus enable better definition of the target volume. To this end, it is advisable to develop alignment, merging and display software tailored to the work of the radiological physicist.

V-2-3 Imaging for control

During a hadrontherapy examination using a carbon ion beam, physical interactions between the ions and the material through which they pass (consisting mainly of water molecules for a human body) cause, as a result of the fragmentation phenomenon, the production of lighter particles such as carbon 11 and 10, nitrogen 14 and 13, oxygen 15, etc. Some of these atoms emit positrons and can therefore be detected by PET. The presence of positron-emitting particles and the use of PET therefore has a dual advantage of being able to follow the paths of secondary particles, and thus calculate the spatial and dosimetric distribution of the primary beam.

PET recording

A PET camera for this recording can be used in two possible configurations: during irradiation (on-line) or after irradiation (off-line).

"On-line" recording has a number of advantages. The first of these is to carry out the recording as early as possible to obtain an in situ image with the best spatial precision. The recording is therefore made during irradiation, between each spill in order to limit the background noise. Secondly, on-line acquisition offers the ability to monitor the distribution of the beam during irradiation and thus modify the treatment at any time from either the spatial or dosimetric point of view. Finally, this configuration makes it possible to limit the signal loss due to the radioactive decay of the isotopes. However, with this configuration it is not possible to obtain good counting statistics due to a very small solid angle and short acquisition time. It is for this reason that this on-line recording approach will require the design of a new system, suitable for the constraints of the hadrontherapy examination.

"Off-line" recording is a much simpler solution in that a commercial PET camera can be used. Although this solution has the advantage of an acquisition time that can be much longer, as it is carried out post-irradiation, it suffers from the absence of in situ information and immediate feedback during irradiation. Moreover, the potential movement of the organs after irradiation and the change in the distribution of the isotopes during this period may prejudice the spatial precision of the information.

A clinical dosimetry tool

The detection of an image of positrons thus makes it possible to draw up the cartography of the fragments and thus calculate (using appropriate modelling) the distribution of the primary beam and also the dose deposited in the target volume. However, this work is complex and depends on the precision of the model used. The model must, using precise simulations, take into account the fragmentation and stopping processes, and the radioactive constants of the primary and secondary particles, in the non-uniform environment of exchanges of the human body. This modelling will correct, amongst other things, the effects of attenuation of transmission and of detection of the g rays.

For on-line recording, a PET camera adapted to the requirements of hadrontherapy is necessary, i.e. with better sensitivity in view of an imperfect geometry. To place the camera around the patient during irradiation while allowing the axis of the beam to pass, a special detection ring will have to be devised. In view of the small solid angle and the low intensity of the beam of secondary particles, a much more sensitive system than those currently on the market will be necessary.

To this end, we propose to develop a new generation tomograph within the context of the Crystal Clear collaboration. The use of new technologies such as avalanche photodiode arrays (APD) and scintillating materials (LSO, LuAP) which are more dense, faster and brighter will make it possible to achieve better sensitivity. Moreover, innovations in software for reconstruction and for measuring the depth of interaction (DOI) using two rows of scintillating crystals with different characteristics will enable the spatial resolution to be improved. Finally, Monte-Carlo simulation studies will provide realistic data to integrate the new characteristics of this prototype.

V-3
Equipement in the treatment and other associated areas

In accordance with the medical specifications, each treatment room has been equipped differently but all future installations remain possible to incorporate technical developments, in particular in patient positioning and imaging. It will be possible to set up a passive dose distribution system in all the rooms in place of the active distribution system.

The systems for measurement of the doses deposited (ionization chambers), the robot-controlled systems for positioning the patient's bed or chair, the X-ray imaging systems and the laser or optical measurement apparatus are all identical, in order to minimise the specific training for hospital staff and to maintain uniformity and inter-changeability of operations.

Optical systems installed in the treatment room will be used for supplementary control of all positioning operations (patient, bed, chair, water phantom and zero or resting point of the robot) with respect to those determined by laser beam.

Each room will be equipped with a support robot which can position a bed, a chair or a beam control device (phantom) in six axes (x, y, z, ρ, θ, ϕ).

As in conventional radiotherapy it is intended that all the immobilization systems will be made on site.

The patient pre-positioning rooms and irradiation control rooms will have identical equipment.

In order to have access to all the necessary diagnostics before or after irradiation, a MRI system and a CT scan will be necessary. A PET camera to check that the distribution of the dose in the target volume complies with that specified in the treatment plan will be provided in one of the treatment rooms. The Lyon hospital environment will provide additional clinical diagnostics to that provided in the centre.

Table V-1 lists the equipment necessary for three treatment rooms and the associated technical areas.

Description	Equipment
Treatment plan room 1	2 planimetry consoles
Treatment plan room 2	2 planimetry consoles
Computer storage and archive room (images, etc)	Planned in the control system
Pre-positioning room 1	Lasers, mobile support table + trolley
Pre-positioning room 2	Lasers, mobile support table + trolley
Pre-positioning room 3	Lasers, mobile support table + trolley
Clinical MRI room	MRI system and accessories
Simulation scanner room	Scanner and accessories
Anaesthetics room + associated areas	Scanner and accessories
Treatment room 1	3 mobile X-ray tubes with image intensifiers Optical system ("Optotrack" type) Lasers Robot, Bed, Chair Passive mode irradiation device Quality control equipment
Treatment room 2	3 mobile X-ray tubes with image intensifiers Optical system ("Optotrack" type) Lasers Robot, Bed, Chair Suitable PET camera Quality control equipment
Treatment room 3	3 mobile X-ray tubes with image intensifiers Optical system ("Optotrack" type) Lasers Robot, Bed, Chair Quality control equipment
Irradiation control room 1	2 stations and associated equipment
Irradiation control room 2	2 stations and associated equipment
Irradiation control room 3	2 stations and associated equipment
Immobilization device preparation room	Specialist machines and tools
Workshops and technical areas	Machine tools, etc
Offices	Equipement
Meeting room	Equipement

Estimated capital expenditure for three treatment rooms: 8.23 M€ (November 2001 cost, excluding value added tax)

Table V-1: equipment necessary for the treatment rooms and associated technical areas

•VI •

Capital costs, development program, development staff

VI-1
Capital costs

The estimates given below are presented in a summarised form. They have been prepared in detail (while remaining in the context of a preliminary design):

• by analysing the sub-systems which have been studied in other projects (HICAT injector, PIMMS synchrotron),
• by the detailed study of new points (beam lines, control system, computer systems),
• by consulting specialist companies or experts for each constituent part (price of magnetic elements, vacuum elements, HF elements, diagnostics). The building, the soil composition of the reference site and the infrastructure (air conditioning, mains power supply) have been analysed in specific studies with the assistance of specialist consultancies and the Property Department of the CNRS.

A global additional cost for contingencies has been incorporated.

A "development staff" item is included in the estimates. This is the project management team and the specialists required for the design and engineering work, the initiation and monitoring of contracts, acceptance, assembly, tests and finally commissioning of the installation. These staff, as for any accelerator, will be present on site during construction. This item does not include the labour required for building the elements of the accelerator as it is included in the services supplied by the manufacturers.

Description	Capital expenditure excluding value added tax November 2001 prices scenario without rotating isocentric gantry (M€)	excluding values added tax November 2001 price isocentrique gantry(M€)
Production of ions, linear accelerator and low energy beam lines.	8.83	8.83
Synchrotron	6.45	6.45
Beam distribution and scanning system	4.68	10.21
Control	8.25	9
Building and infrastructures (including project management)	23.2	24.6
Equipment for rooms	8.23	8.23
Cost of development staff	15	15
Contingencies 7%	5.22	5.74
Total cost (M€)	**79.86**	**88.06**

Table VI-1: capital costs

Note: The "building and infrastructures" line includes a system for protecting important equipment against mains power failures (HQPS subsection XI-2-1 in volume II), for a cost of 0.7 M€.

VI-2
Development program

The development is based on a six-year program including a detailed design stage of about two years. The graph below presents the total capital expenditure plan, including staff and equipment (figure VI-1). The scenario shown is that with a rotating isocentric gantry. The main expenditure is as follows:

- the contract relating to the project management of the building will be initiated in the first year.
- the funding of the building and entire infrastructure will be initiated in the second year.
- the funding of most of the main equipment (high technology components) will be initiated in the third year.
- the funding of the control system will be initiated in the fourth year, together with that of part of the medical equipment.
- the capital expenditure in the fifth year will be devoted to the remainder of the medical equipment.
- the sixth year will be devoted to machine testing ("pre-clinical" period) and validation of the treatment system and to administrative licensing for treatment. This year corresponds to "year 0" of the centre's increase to full capacity, during which the first patients will be treated.

The possibility and methods of collaboration with organisations, either French (the CEA or CNRS laboratories for example) or European (CERN, GSI, TERA), must be anticipated in order to take advantage of their considerable experience (synchrotron aspects for CERN and TERA, injector for GSI, for example).

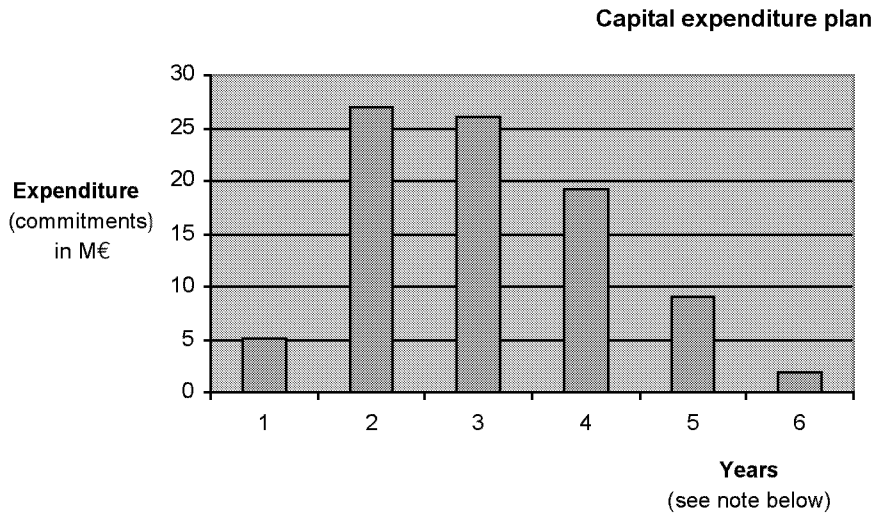


Figure VI-1: capital expenditure plan, including staff and equipment (including 7% for contingencies) for a scenario with rotating isocentric gantry

Note: year 1 is the year of the decision in principle to go ahead with ETOILE. Year 2 is the year of the final decision. Year 6 is "year 0" of the centre's increase to full capacity, during which the first patients will be treated.

VI-3
Development staff

The following graph shows the planned numbers of staff managed directly by the project and required for its development (figure VI-2).

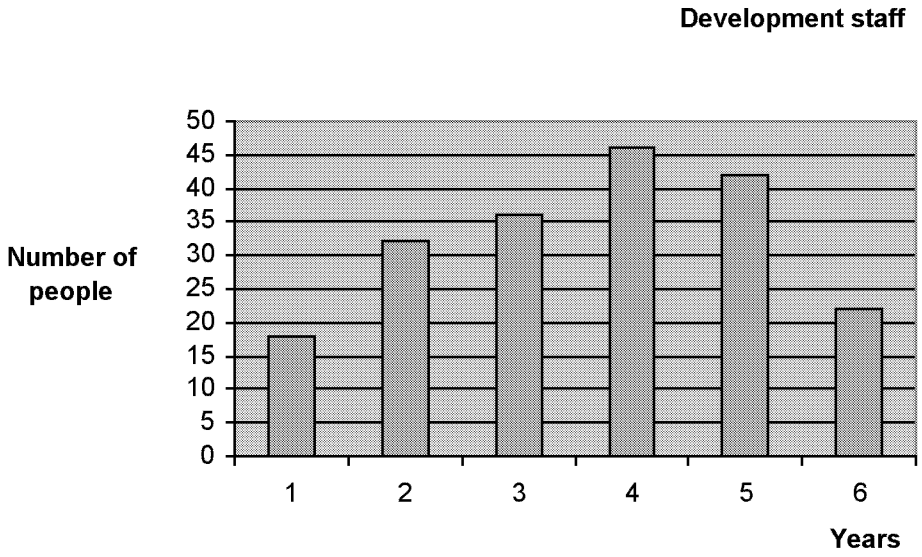


Figure VI-2: staff involved during the development phase

The "responsibility for development" cannot, in our opinion, be totally assigned to one manufacturer which would have to guarantee the performance of an immediately usable installation which it had never built before. The same argument has been used in the Heidelberg project.

• VII •

Operating scenarios and needed staff. Running costs

VII-1
Scenarios of increase to full capacity and routine operation

A gradual increase to full capacity over three years is envisaged in terms of recruitment and treatment of patients. As well as the checks of the irradiation beam, this increase must allow treatment procedures and quality procedures to be set up and monitored in a way which is totally safe for patients. It will also allow for the training and recruitment of care staff, leading to a final daily operation with two shifts of care and technical staff, for 1000 new patients treated per annum in three rooms.

VII - 1 - 1 Increase to full capacity

The scenario envisaged for the increase to full capacity in terms of patients and medical and technical teams is as follows:

"Year 0": first patients
- Corresponds to the "handover" of the synchrotron, with control of the beams, radiobiological research and setting up of therapeutic procedures. The first patients will be treated
- Limited medical team, consisting of two medical physicists and 0.5 to 1 full time equivalent doctor-researcher (radiobiological tests)

1st year: 75 patients
- Two treatment rooms: one room with a fixed horizontal beam and one room with either a gantry or a vertical beam (and possibly an horizontal beam)
- One medical team and one technical team
- Phase I and II clinical trials

2nd year: 350 patients
- Three treatment rooms: two rooms with a fixed horizontal beam and one room with either a gantry or a vertical beam (and possibly an horizontal beam)
- One medical team and one technical team
- Phase I and II clinical trials

3rd year: 750 patients
- Three treatment rooms: two rooms with a fixed horizontal beam and one room with either a gantry or a vertical beam (and possibly an horizontal beam)
- Two medical teams and two technical teams
- Phase II clinical trials and start of randomised comparative studies (phase III)

4th year onwards: 1000 patients
- The potential number of annual irradiation sessions is based on the following assumptions: 220 days of actual treatment, 11 hours per day for each treatment room, 30 minutes average duration of a session, i.e. around 15 000 sessions.
- The potential number of annual patients is based on the following assumptions: 50% of patients treated with 20 sessions of carbon ions only, and 50% of patients treated with a combination of photons (outside the hadrontherapy centre) and 10sessions of carbon ions, i.e. an average of 15 sessions per patient.
- Optional prospects of increasing the number of patients depending on the possibilities of hypofractionation, progress made enabling the duration of each session to be reduced, and modification of the time slots.

It is anticipated that 90% of treatments will be carried out on day patients, with no hospitalisation. Arrangements for local accommodation will be proposed. About 10% of patients will have to be hospitalised in care facilities close to the hadrontherapy centre.

VII-1-2 Routine operation
Operating scenario of the centreI

5 days worked per week, i.e. 260 per annum. 44 weeks will be devoted to treatment i.e. 220 days. 10 days each year will be public holidays (fixed or movable).

The remaining 30 days will be used for preventive maintenance and a number of machine tests (updating of equipment, improvements, re-certification). This could correspond to 7.5 days stoppage every 3 months, with, for example, 5 days preventive maintenance and 2.5 days of machine tests.

The days will be 14 hours long, i.e. 2 shifts (35 hour weeks)

Adjustments and certification from 6 am to 8 am (duration: 2 hours)
Treatment from 8 am to 7 pm (duration: 11 hours)
Post-treatment checks 7 pm - 8 pm (duration: 1 hour)

Session duration: 30 minutes

Number of sessions

The centre will have three rooms. Treatment will be carried out 220 days a year, for 11 hours per day, thus providing 14 520 treatment sessions, enabling 1000 patients to be treated (see above).

Medical and radiobiological research

The machine can be used outside the daily operating hours (3 hours of certification and 11 hours of treatment, 5 days a week) for specific studies in the field of medicine and radiobiology. However, in this case, the working hours of the technical staff will have to be re-organised.

VII-2
Centre staff

VII-2-1 Technical staff

With these assumptions for operation, the technical staff requirements are estimated below.

The experience of GSI indicates that it is necessary to have machine operation expertise available during the treatment period, at the treatment room consoles, as well as the operator (medical staff). It is assumed that during this period, the "main" machine console is on standby to monitor the parameters.

Operation - Morning shift

A technical manager must be present.
A system manager must be present, in view of the high degree of automation of the centre.
Adjustment and certification phase: two operators at the main console
Treatment phase: one of the operators will be available for the three rooms. The second operator will remain at the main console.

Total: 4 people.

Operation - Afternoon shift

The scenario will be similar for the afternoon shift, replacing the adjustment phase with the checking phase.

Total: 4 people.

Staff not assigned to a shift

In order to provide constant servicing and in particular first level repairs in periods of under an hour, the following staff will be distributed over the two shifts:
Radiofrequency, diagnostics, sources: one engineer and one technician
Vacuum, electromechanics, mechanics: one engineer and one technician
Power electronics, electronics: one engineer and one technician
Night watch: two technicians (this is the minimum as the watch period is 10 hours)

Total: 8 people

General total: seven engineers and nine technicians, i.e. 16 people.

This is a minimum number which gives an average of 5 to 6 technicians at the centre, for the 5-day 35-hour weeks worked. It does not include any overlapping of technical teams or time for training, or holidays. However, it is assumed that the machine will be sufficiently reliable to enable overlapping and include holidays.

VII-2-2 Medical staff: qualification - activity

Data concerning the medical staff is given in table VII-1

For the medical team, a high assumption for France has been made. The number of members of staff takes into account the chosen operating scenario (5 days per week, 2 shifts per day) and current labour legislation. The "full time equivalent" (FTE) numbers for the medical team are given for each type of activity. Due to the extremely technical nature, the importance of the evaluation (clinical, radiobiological, dosimetric, etc, research) and the necessary university component of such a centre, the "physician" and "physicist" times devoted to an activity other than treatment (research, teaching) have been estimated to be 50%.

The figures given agree with (and are lower than) those for the German and Swedish projects.

Nature	Total ETP	Treatement	Research	Teaching
Medical doctors	12	6	3.6	2.4
Physicists	9	4.5	2.7	1.8
Dosimetrists	4	3.2	0.6	0.2
Operators	19	15.2	1.9	1.9
Supervisors	1	0.8	0.1	0.1
Porters	2	2		
Nurses	3	3		
Reception staff	3	3		
Secret. Admin.	5	5		

Table VII-1: data for medical staff (in FTE)

Due to the specific features of such a centre engaged in clinical, biological and technological research, the activities connected with treatment, research and teaching have been given separately for each category of staff. The proportion of time spent on treatment will, of course, increase during the phase of the increase to full capacity in terms of patient recruitment and time slots. The activity may be divided unequally within one professional category, depending on the responsibilities of each individual.

Radiotherapists

1- Activity connected with treatment:
- Recruitment, treatment and follow-up of patients. Organisation of weekly (multidisciplinary) departmental meetings to present cases (in particular via a network of images).
- Definition of volumes to be irradiated and validation of the planimetry in collaboration with the physicist, and daily monitoring of treatments.

2- Research and teaching activity
- Clinical research (protocols, evaluation, etc.)
- "Basic" research: radiobiology; imaging, etc.
- Teaching, visits ../...

3- Administrative activity: one co-ordinating physician

Medical physicists
1- Activity connected with treatment
- The physicist is responsible for the quality of the irradiation via the checking of the beam (2 hours per day) and the checking of each new treatment. The physicist is responsible for the planimetry, in collaboration with the physician.
2- Research and teaching activity
- Radiobiology; imaging; computer science
- Teaching, supervision of PhD students
3- Administrative (1 assistant departmental manager?)

Dosimetrist
This activity is mainly connected with treatment, reporting to the physicist (preparation of the planimetry and beam control)

Supervisor (radiology operation team)
The supervisor is involved in the activity connected with treatment, and has an administrative (supervision of the operators) and teaching function

Medical-technical assistants
The activity is mainly connected with treatment.
1- "Treatment preparation" (1 station)
1 team of 3 members of staff is required for:
- Making the immobilisation devices, setting up and teaching the respiration control system to the patient
- Scanner imaging and MRI (and possibly PET), preparation for planimetry
2- "Performing treatment" (3 stations: 3 treatment rooms)
7 to 8 members of staff per shift are necessary for carrying out treatment:
- Pre-positioning of the patient (putting the immobilisation device in place in the "pre-positioning" room) during the irradiation of the previous patient and laser or Radiology. checks
- In the treatment room: control of the positioning (laser and X-rays), installation of the respiration control system before validation by the radiotherapist
- Monitoring the patient during irradiation
- On-line PET (research project)

Porters
(2 present per shift at least one shift a day)
- Assistance with pre-positioning, and taking patients to the rooms
- room cleaning

Medical secretaries
- Management of appointments, treatment reports, administrative duties

Nurse
1 present 7 to 8 hours per day
- Replacing dressings (assistance with consultations)

Receptionists
1 or 2 present each shift
- Patient welcoming and directing, administrative paperwork

Administrative staff
1 centre manager
1 general secretary
1 secretary or 2 administrative assistants
3 management secretaries

VII-3
Costs connected with technical operation

These are estimated annual values, based on 2001 prices, in M€ excluding value added tax (excluding staff)

Electricity	0.70
Fluids	0.08
Maintenance of infrastructures	0.23
Maintenance of buildings	0.09
Maintenance of the accelerator	0.83
Accelerator improvements, updates	0.43
Development of medical software and equipment	0.23
Fixed costs (land, insurance, security, etc)	0.22
Total	**2.81 M€**

Table VII-2: costs connected with technical operation

VII-4
Running costs

The cost of the project will be the total of three costs:

- staff costs
- capital expenditure costs
- technical operating costs

The increase to full capacity is taken into account.

VII-4-1 Staff costs

The activity of the medical teams has been broken down into three items: activity connected with the treatment itself, research and teaching.

The production column which essentially describes the activity connected with treatment indicates what the routine "net" operating cost of such a centre would be without research and teaching.

Appendix X-3 gives detailed staff costs.

Table VII-3 summarises the total salary costs* (production of treatment, research and teaching) and their division between technical and medical team costs.

Year	Number of patients	Total cost in (k€)	Technical team	Staff cost per patient (in k€)	Staff cost per patient (in k€)
0	a few	684	488	197	
1	75	2 305	831	1 474	30.73
2	350	3 029	1 121	1 909	8.65
3	750	4 474	1 121	3 353	5.97
4 onwards	**1000**	**4 474 k€**	**1 121**	**3 353**	**4.47 k€**

* November 2001 prices

Table VII-3: total staff costs

If only the cost of activity connected with treatment is used for the medical teams, the "net staff cost per patient" (excluding research and teaching) then becomes:

Year	Number of patients	Net staff cost (in k€)	Technical team	Medical team	Net staff cost per patient (en k€)
0	a few		488		
1	75	1 511	831	680	20.15
2	350	2 177	1 121	1 056	6.22
3	750	3 332	1 121	2 212	4.44
4 onwards	1000	3 332	1 121	2 212	3.33

Table VII-4: net staff cost per patient (for information)

VII-4-2 Capital expenditure costs

The capital expenditure cost (detailed in VI-1) is 88.06 M€ excluding value added tax (assumption with gantry) which can be broken down into:
- 26.32 M€ for the building
- 61.74 M€ for the equipment.

The loan repayment costs will depend on the full amount of grants obtained and the pay-back periods.

Two assumptions for the full amount of grants obtained have been considered (foot note):

- 25 M€
- 50 M€

And three assumptions for the loan pay-back periods:
- 20 years
- 25 years
- 30 years

These assumptions are simulated in table VII-5, using an interest rate of 5%.

	20 years	25 years	30 years
25 M€grant Cost to be funded: 63.06 M€	5.03	4.46	4.09
50 M€ grant Cost to be funded: 38.06 M€	3.03	2.68	2.46

Table VII-5: annual loan repayment costs

Note: in these two hypotheses the numbers are intentionally lowered in order to avoid underestimating the operating cost.

VII-4-3 Technical operating cost

This has been given in detail in VII-3 and is repeated here:

Costs	M€*
Total technical operating cost	2.81

Table VII-6: Annual technical operating cost

VII-4-4 Structural deficit before reaching full capacity

The first four years of increase to full capacity will generate costs greater than the "revenue" connected with the treatment activity.

• Costs: These costs are repeated below (39.57 M€).
• Revenue: The treatment activity of the first four years corresponds to: 0+75+350+750 = 1175 patients. The value of this activity can be estimated (assuming 14 k€ per treatment) at 1175x14 = 16.45M€.

Years	0	1	2	3	Total
Staff costs	0.684	2.305	3.029	4.474	10.492
Technical operating costs	2.81	2.81	2.81	2.81	11.24
Repayment of loans (base 25 years grant 25 M€)	4.46	4.46	4.46	4.46	17.84
Total cost	7.95	9.58	10.30	11.74	39.57
Revenue	0	1.05	4.90	10.50	16.45
Deficit	7.95	8.53	5.40	1.24	23.12

Excluding value added tax, November 2001 prices

Table VII-7: structural deficit before reaching full capacity (in Mg)

VII-4-5 Summary total running cost

Paying back all the costs of the four years up to the increase to full capacity in the routine years gives the following total running cost:

Payback period	20 years		25 years		30 years	
Grants (M€)	25.00	50.00	25.00	50.00	25.00	50.00
Cap. exp. to be funded (M€)	63.06	38.06	63.06	38.06	63.06	38.06
Initial deficit to be funded	23.12	23.12	23.12	23.12	23.12	23.12
Repayment of loans	5.03	3.03	4.46	2.68	4.09	2.46
Technical operating cost	2.81	2.81	2.81	2.81	2.81	2.81
Staff cost	4.47	4.47	4.47	4.47	4.47	4.47
Payback of initial deficit	1.84	1.84	1.63	1.63	1.50	1.50
Total (M€)	**14.15**	**12.15**	**13.37**	**11.59**	**12.87**	**11.24**
Number of patients	1000	1000	1000	1000	1000	1000
Running cost per patient (k€)	**14.15**	**12.15**	**13.37**	**11.59**	**12.87**	**11.24**

Excluding value added tax, November 2001 prices

Table VII-8: total running cost in a "routine year"

• VIII •

Funding" and "management-organisation" considerations

VIII - 1
Funding requirements and potential funding

This section gives the elements of the financial consideration. This will be examined in detail with potential funders, using this document as the base.

Table VIII-1 summarises the specific funding requirements for the capital expenditure (see § VI-1) and for the initial deficit (first four years). See § VII-4-4.

	Low assumption	High assumption	Comment
Capital expenditure	79.86 M€	88.06 M€	Of which 24.82 to 26.32 M€ is for building. These numbers include 7% for contingencies
Initial deficit	23.12 M€	23.12 M€	first 4 years
Total funding requirement	**102.98 M€**	**111.18 M€**	

Excluding value added tax, November 2001 prices

Table VIII-1: specific funding requirements for the capital expenditure and operation in the first four years

Table VIII-2 outlines the type of funding requirements, their timing and the potential sources of funding. The comments qualify the concept of "potential source of funding.

Type of requierement	Year								Funding
	0[9]	1[10]	2[11]	3	4	5	6[12]	7	
Preliminary design	x	x							MR, CL, OR, A, U
Capital expenditure		x	x	x	x	x			MR, OR, NS, CL, F; E
Operation "Initial deficit"							x	x	
Operation "Research"	x	x	x	x	x	x	x	x	MR, OR, NS, RA, E
Operation "Treatment activities and associated operation"								x	NS, RA

Table VIII-2: types of funding requirements

[9] Year 0 is 2001
[10] Year 1 is that in which the decision in principle will be made to go ahead with ETOILE. The invitation to tender for the project management of the building will have been published, the total cost of the project management contract will have been established.
[11] Year 2 is that in which the final decision will be made. The funding for the building and the entire infrastructure will be established.
[12] Year 6 is the first year of the increase to full capacity of operation.

Comments

Studies

A total of 3.17 M€ has been obtained, 2.90 M€ of which is from the CPER (State-Region Spending Plan). Part of this amount will be used to fund studies connected with the preliminary design, the first years of the project team and the initiation of specific research and development. The remainder will be allocated to detailed design work.

The sources of funding are:

(A) Anvar (0.06 M€)
(U) Université Claude Bernard Lyon1 – UCBL (0.06 M€)
(MR) Ministry for Research (0.75 M€)
(CL) Rhône-Alpes Region (1.27) and Metropolitan Authority of Lyon (1.10 M€)

NB: The CNRS, the CEA and the UCBL are indirectly involved in funding by invoicing for the time of the experts carrying out the studies at reasonable prices.

Capital expenditure

A medical facility, the scale and innovative nature of which are virtually unknown, poses a specific problem for funding the necessary capital expenditure. The following points are aimed at opening up the field of possibilities.

-NS (**Organisms in charge of National Health**).
The FIMHO participates in the funding of projects centred on hospital modernisation. The ETOILE project could benefit from this, by extending its field (and its financial size).
A small part of ONDAM is reserved for nationally orientated allocations. A new national allocation could be assigned to hadrontherapy.

-MR (**Ministry for Research**). As this involves an innovative facility for a new therapy, and for medical research and associated technological research, the Ministry for Research - which is already involved in funding the design - is a significant potential financial partner for the "equipment" part of the capital expenditure (and for the operating/research part).

-RO (**Research Organisations**). The CNRS (IN2P3, STIC, SPI, Life Sciences), the CEA (DSM, DSV) and INSERM (even the INRIA) are, by the same logic, potential financial partners, after consultation.

INSERM (even the INRIA) are, by the same logic, potential financial partners, after consultation.

-CL (**Local authorities**). The Rhône-Alpes Region, like the Metropolitan Authority of Lyon, have (at the beginning of the CPER and after) demonstrated their strong commitment to this major high technology facility located at Lyon. It strengthens the Health sector, which is a priority in the region's development plan. They are likely to be significant financial partners. The Conseil Général du Rhône (Rhone General Regional Council), which has recently had to face new costs, seems reluctant to take on new commitments.

-E (**Europe**). The 5 contemporaneous projects at Heidelberg, Milan, Stockholm, Vienna and Lyon constitute a strong, innovative European project. One of its first events was the creation, in October 2001, of the "ENLIGHT" subject-based network, already funded by the 5th PCRD (Research and Development Framework Programme) at the beginning of 2002, and which will present an integrated project for the 6th PCRD.

-F (**financial bodies**). A loan from the sources of funding to local authorities (CDC, Dexia, etc) would be possible. Insurance companies and mutual health societies could also be interested.

Security for loans should be considered (Region, etc).

Operation

This new structure will be unable to balance its budget during the time needed to reach full capacity of operation. The corresponding deficit should be specifically funded.

The operating budget of the centre will have a relatively large research component – in particular in the first few years - and a medical component. Potential sources of funding are:

-MR (**Ministry for Research**): cf. above in "capital expenditure". It is desirable that its contribution involves a structural part which lasts several years and a part to be called upon for projects.

-RO (**Research Organisations**): cf. above in "capital expenditure". It is also desirable that they are institutional partners (see VIII-2 "management-organization") and scientific partners of the Centre, assigning it staff and credits. This involvement has already started with the research and technical staff involved in the setting

up of research projects the objectives of which will be devised with these research organisations.

-E (**Europe**): cf. above in "capital expenditure". ETOILE and the other similar European projects will submit projects together in the framework of the 6th PCRD and will seek other methods of assistance from Europe.

-NS (**Organisms in charge of National Health**). The financing of clinical research will take place mainly when the centre is operating.

It is essential that, from its creation, the ETOILE centre is recognised and has a budget within an appropriate institutional framework (see IX-2 "management-organisation"). This budget will cover part of the research as is normal.

-AR (Attenuating Revenue). ETOILE will seek to maximise its "attenuating revenue" and in particular its own resources. Involvement of the Ligue contre le Cancer (League against Cancer), the ARC (Association pour la Recherche sur le Cancer - Cancer Research Association), and other Foundations will of course be sought. The centre will open its doors to French and European practitioners (radiotherapists, organ specialists, radiological physicists, operators, etc) as a centre for advanced training and scientific exchanges, involving the manufacturers who may be concerned.

VIII - 2
Management-organization

The role of ETOILE, a national centre which is located regionally, in the organisation of Hospital-based Health will be the subject of joint discussions on:

- the management structure of the centre
- the coordination of French hadrontherapy
- the method of budget allocation

1 - The location of the centre in a region with a high university hospital capacity allows the establishment **of a management structure for the ETOILE Centre which combines** the main hospitals (Lyon, Grenoble and St Etienne University Hospitals, Regional Anticancer Centre Léon Bérard, etc) and which can be open to the private sector.

The strong research component leads naturally to an expected involvement of the relevant national research organisations.

Certain sources of funding (insurance companies, etc) may request to be involved in the management.

The national aspect must be clearly represented - in particular by the overall "hadrontherapy" structure (see below).

This management structure may be open to change with respect to its legal form: initially it will involve carrying out detailed (medical and technical) design work and the creation of the Centre, and the coordination of research and development. An Economic Interest Grouping (GIE) may be considered. Subsequently it will involve the management of a treatment centre and the coordination of research and development. The detailed functional analysis will be undertaken soon.

2 - ETOILE will be a national centre, providing a new form of radiotherapy alongside external photon radiotherapy and current proton and neutron hadrontherapy. Care must be taken to ensure the coherence of the national setting and thus the clinical indications appropriate for each therapy, and **in particular to optimise the objectives of each hadrontherapy centre (Orléans, Orsay, Nice, Lyon, etc)** and their efficacy. ETOILE will be involved particularly via the first phase in the thesis work of a radiotherapist at the Centre Léon Bérard – a thesis on the medico-economic evaluation of therapeutic innovations (Laboratoire d'Analyse des Systems de Santé de Lyon - Lyon Health Systems Analysis Laboratory).

This consultation will enable coherent planning of the evolution required in particular in heavy equipment.
This clinical and strategic consultation will be accompanied by essential **scientific and technological consultation** between the hadrontherapy centres (and the associated research teams), covering, for example, modernisation of planimetry software, positioning robots and the associated software, positioning control, modelling and movement control software, clinical research in radiobiology, mixed photon-hadron treatment protocols, etc. This work, with the support of the national research organisations, will have a major impact in stimulating and producing concrete spin-offs in the field of radiotherapy, which is and will remain for some time to come the second method of therapy for treating cancers, after surgery.

This argues for the emergence, in one or more stages, of an overall national "Hadrontherapy" structure which brings together the four Centres mentioned above, and the national organisations involved in research and health.

3 - As far as funding is concerned, the ETOILE project poses specific problems, because the national budgetary system is based on the regional distribution of budgets. The recruitment of patients, which will initially be regional, will necessarily expand once the feasibility has been established and the preliminary results published, to cover to all regions, and also bordering European countries.
This is a major facility with a considerable annual budget, which due to its centralised and innovative character, will not be without uncertainties in its recruitment of patients and its "throughput", and it must be certain that the creation of ETOILE will not be a source of fear or reduction in the budgets of the hospitals in the Rhône-Alpes region.

The method of budgetary allocation must take these specific aspects into account. These aspects will be analysed in 2002, with the health authorities and the existing hadrontherapy centres. The institutional solutions which are introduced may be totally or partly based on the overall national structure mentioned above.

• IX •

Conclusions

IX-1
ETOILE is based on strong convictions

-Cooperation between physicians and physicists and the future of radiotherapy, including hadrontherapy.

This cooperation is too rare and has, in particular, made France dependent to abroad, both scientifically and industrially, for its radiotherapy and imaging medical equipment. The challenge for this co-operation, which has brought about the creation of this project, is the challenge of the future of imaging and, above all, **the reasoned challenge of the future of radiotherapy** in France. Although its end was predicted at the advent of cytotoxics, still more than a third of cancer cures are due to radiotherapy (alone or in association). It is admitted now that radiotherapy has a considerable potential for progress.

The progress made in the screening for non-metastatic cancers and advances in the treatment of metastatic disease will increase the indications for radiotherapy treatment. From the limited number of discussions which have been initiated with specialists in molecular and genetic therapies, there is a consensus which can be summarised as follows: "it is very probable that, for several decades to come, in order to face the wide heterogeneity of cancers a wide diversity of therapeutic techniques will be necessary, including external irradiation and brachytherapy".

Carbon ion hadrontherapy is potentially applicable to 18, 000 cases of cancer per annum in France today and this number will probably increase.

-European co-operation

International co-operation is evident in the world of cytotoxics and gene therapies (research networks). It is essential for the European ETOILE type projects, **at a technological level** (around CERN in particular) and even an industrial level, bringing together the best expertise and energising research and development which will help bring about innovations. Above all, European co-operation is essential at **a clinical level** since only with close co-ordination will it be possible to rapidly validate the therapeutic protocols including carbon ions for the indications for which they are intended.

-National co-operation

The ETOILE project must fit in the framework **of a coherent national policy of modernising the fight against cancer using radiotherapy (photons and hadrons)** which is part of the 2000 French nation cancer plan: the modernisation of conventional radiotherapy facilities must be seen through to a successful conclusion in the coming years, with the arrival of ETOILE representing a "new stage in the process".

This stage is foreshadowed in the current French hadrontherapy centres, Orléans for neutrons, Orsay and Nice for protons. **Consideration and discussion** on French hadrontherapy, bringing together these centres and the ETOILE project is starting to take place, with the aim of setting up a coherent plan for the future, based on a critical analysis of their experience and projects (and experience and projects in other countries). This plan will include the target tumours for each centre, the target populations and the recruitment of patients, the costs, the methods of funding, the development of the centres, the facilities and the protocols, the technological and medical research, etc. This work will naturally include the future ETOILE centre.

Furthermore, it is clear that this work must be based on experience gained in the current hadrontherapy centres (some of the specialists from these centres have contributed to the ETOILE research programs) which are part of the European ENLIGHT project.

This synergy, and the questions concerning the funding of these regional, national and European centres, argue for the setting up of an overall national "Hadrontherapy" structure, the legal form of witch will only be possible to discuss after an indepth functional analysis has taken place.

All conventional radiotherapy will benefit from this approach. The ETOILE project will find an additional - and important - justification in the positive spin-offs which will appear for conventional radiotherapy in terms of revitalisation of the image of modernity and in terms of stimulation of clinical and radiobiological research and well as technological research and development and its implementation (positioning, planimetry, imaging). It must be remembered that ETOILE will work, in terms of receiving patients, as part of a network with a number of other French and European conventional radiotherapy centres with a high level of reciprocal requirements and exchanges.

-Regional co-operation

Regional co-operation has existed since the start of the project, as seen by the fervent commitment of each individual and organisation. The expertise of the scientific and universities and the Lyon, Grenoble and Saint Etienne University Hospitals and the Regional Anticancer Centre Léon Bérard, together form a large unit which cooperate with one another due to a strong involvement in the region. The proximity of the International Agency for Research on Cancer (IARC) in Lyon and CERN in Geneva is an obvious benefit.

This regional unit clearly intends to provide France with a strong project in a European context. Various different actions have already been initiated and have demonstrated that this regional unit can act as a unifying nucleus at a national level, which is capable of working in partnership with other European units.

IX-2
ETOILE is carrying us into the future

The strength of this project lies in the hope it will bring for the coming decades in the improvement in the treatment of cancerous tumours. It represents a significant step forward in the effectiveness of radiotherapy, which is, and will remain for sometime to come, a major weapon in the fight against cancer, alongside the surgical, pharmacological, and one day, genetic, weapons. The difficult progress of this fight and the heterogeneity of cancer, show that these weapons are clearly complementary at the moment and will remain so for the foreseeable future.

It is also possible that other centres of a similar type to ETOILE will follow: the Germans are already talking about one.

The strength of this project lies in its potential consequences:
- on European co-operation in medical technology. The ETOILE project is based on the considerable scientific expertise of physicists - in particular nuclear and particle physicists - developed at a European community level (CERN is well recognised throughout the world), at a French national level and at the level of the countries running sister projects. Their applications in the medical field could enable Europe to regain some of the ground it has lost in the field of medical facilities.

- on European co-operation in the fight against cancer. It will be indispensable for the coordination of the clinical trials for validating the therapeutic protocols including carbon, involving radiotherapists and organ specialists. This necessary joint work will enhance the value of the existing European networks.

- on the revitalisation of radiotherapy in France. If the modernisation of its facilities has fortunately started, and as a consequence its restructuring, a clear signal by the decision to start ETOILE would be welcomed as increasing the standing of this field, revitalising the recruitment and training of radiotherapists and radiological physicists, as well as medical research and technological research and development. The network of hadrontherapy centres which ETOILE will reinforce will constitute a strong nucleus.

- on the process of decentralisation in France. It is clear that the location at Orsay, for example, of a carbon ion hadrontherapy centre could be strongly justified in terms of expertise or potential market close by. The choice of Lyon/Rhône-Alpes will be part of the desire for the emergence in France of strong national centres, in the regions, working in a network.

- on the dynamism of the Rhône-Alpes region in multidisciplinary research for health, carried out cooperatively. The increasing involvement of regional computing expertise, and above all physics expertise - based on the major facilities at Grenoble and CERN and at an international level - will bring about certain progress, for example in medical imaging - as will the "PET" project associated with the ETOILE project.

- on the choice of Lyon establishing itself as a centre of excellence and innovation in the field of health, and particularly in that of cancer, making use of the European potential provided by all the local establishments: the Hospices Civils de Lyon, the 2nd largest university hospital in France, the Centre de Lutte contre le Cancer Léon Bérard, the Centre d'Exploration et de Research Medicals par Emission de Positrons, the International Agency of Research on Cancer. This potential is strengthened in particular by the active proximity of Grenoble.

The attraction of Lyon and the Rhône-Alpes region for innovative companies in the bio-medical and bio-engineering fields will benefit the strong image of ETOILE, just as ESRF has done for Grenoble and Rhône-Alpes.

The geographical positioning of Lyon places the ETOILE French facility at the heart of its potential attraction area in the west of Europe.

• X •
Appendices

X- 1
Research project information sheets and technological development

Project 1: Physical interactions between light ions and living matter
Project 2: Treatment planimetry
Project 3: Positioning and control of the ballistics
Project 4: On-line PET imaging

X-1-1
Project 1: Physical interactions between light ions and living matter

Problem
The principal advantage of light ions is connected with the high ionization of matter at the end of their range (Bragg's peak) which corresponds to an optimal biological effectiveness (RBE), in particular for carbon ions. In addition, they produce ß⁺ emitting fragments which enable them to be located and thus providing the possibility of controlling the dose during irradiation. These specificities require the production of simulation algorithms which include the effects of dose deposition, the nuclear effects and the microscopic effects essential for the simulation of the RBE. These algorithms must be integrated in the treatment planimetry software in the form of modules.

Scientific objectives

1. To extend the algorithms for calculating the paths and penetration of light ions in the specific cases of very high energy deposits (Bragg's peak) in living matter.
2. To introduce nuclear effects during the penetration of the ions: associated positron fragmentation and emission.
- Modelling of the spatial distribution for each isotope produced.
- Experimentation on water phantoms and small animals, with the GANIL beam, using the micro-PET bench scan developed by the Crystal Clear group, Lyon.
3. To model the dose deposited by all the ions using the reconstructed PET image.

Socio-economic spin-offs
Hadrontherapy centres, including protontherapy. Nuclear and space industries, etc.

Laboratories currently involved
IPNL (UMR 5822 UCBL-CNRS), LIGIM (EA 1899 UCBL)

Existing or planned collaboration
GANIL (UMR 6415 CEA-CNRS/IN2P3), CIRIL (UMR 6637 CEA-CNRS-University of Caen), GSI (Heavy Ion Physics Institute in Darmstadt, Germany)

Program
- State of the art: June 2002.
- Widening and structuring of the project group. Start of the project: September 2002.
- 1st stage: Estimate of the size and performance of the current codes: M0+12
- 2nd stage: Construction of a prototype path simulation module: M0+9
- 3rd stage: 1st fragmentation experiments: M0+24
- 4th stage: Improvement and portability of the modules: M0+48

X-1-2
Project 2: Treatment planimetry

Problem
A treatment planning system is composed of a number of elements or modules (imaging, calculation of dose distributions, etc) which are used to define the irradiation parameters.

Existing radiotherapy and protontherapy modules can be adapted for light ions taking care to ensure compatibility with conventional planimetry systems, so that data can be exchanged with a group of partner centres.

The specific characteristics of light ions to be taken into account are their biological effectiveness [74] and the production of β^+ emitting fragments which will enable the on-line control of the dose deposited.

Scientific objectives

1. Using the existing system, develop, adapt or improve planimetry software for photons, protons and carbon ions which can be used, distributed and interfaced with the software used in conventional radiotherapy
2. To improve this software by the integration of:
- extended merging of imaging methods;
- nuclear fragmentation ;
- biological effects (RBE)
3. To improve this software by integrating patient movement

Socio-economic spin-offs
The development of image processing modules (extended merging, integration of movement) will have a direct benefit for conventional radiotherapy. The inclusion of a module for calculating the dose distributions for a light ion beam, that could be interfaced with the other planning systems (photons, protons) would facilitate the exchange of images in the context of a network of partner centres.

Laboratories currently involved
IPNL (UMR 5822 UCBL-CNRS), LIGIM (EA 1899 UCBL), Institut CURIE (CLCC-Paris), Grenoble University Hospital.

Existing or planned collaboration
Collaboration with the Orsay protontherapy centre, with INRIA, with GSI on the TriP software, with the Catholic University of Louvain (Brussels) and with the other projects from the ENLIGHT network. Collaboration with CERN.

Programme
-State of the art: April 2002
-Widening and structuring of the project group.
Start of the project: May 2002
-1st stage: to adapt/improve operational planimetry software, starting with the existing system, which can be used for photons / protons / carbons
-2nd stage: to improve this software by integrating extended merging of imaging methods fragmentation RBE
-3rd stage: to improve this software by integrating movement

X-1-3
Project 3: Positioning and control of the ballistics

Problem
An error in the positioning of the patient may result in harmful effects on healthy tissue and insufficient exposure of malignant tumours. To avoid this error a patient immobilisation system is often used, or light sensors are employed to follow external markers. However, these methods do not provide sufficiently precise positioning.

A better solution would be to use multimodal images, which would provide dynamic monitoring of the organs concerned, combined with marking and precise geometric modelling of the internal structures [75] [76].

Scientific objectives

1. To develop high-performance tools for the alignment and merging of multimodal images (functional and anatomical) for the preparation and control of treatment. Two types of algorithm will be developed:
- real-time for control during treatment
- deferred time for analysis and diagnosis before and after treatment sessions
2. To construct tools to help with the assisted segmentation of volumes to facilitate the task of contouring
3. To develop tools to assist with initial positioning and monitoring of movements. This requires two levels of study:
- control of the position of the patient in relation to the system (development)
- control of the position of the organs in relation to the patient (research)

Socio-economic spin-offs
The results of these studies will contribute to solving problems encountered in conformal radiotherapy, in computer assisted surgery and in 3-D medical imaging.

Laboratories currently involved
LIGIM (EA 1899 UCBL), ERIC (EA 3083 Lyon 2), LASS (UMR 5823 CNRS-UCBL-Lyon 3), TIMC (UJF Grenoble)

Existing or planned collaboration
Northwestern Medical Physics (UK), ELEKTA (UK), Magdebourg University (D) and the members of the European ENLIGHT project.

Programme
• State of the art: M0+6
• Widening and structuring of the project group.
Start of the project:
• Merging and aligning images in deferred time: M0+18
• Merging and aligning images in real time: M0+30
• Segmentation for assisted contouring of volumes: M0+24
• Initial positioning and monitoring of the patient's movements in relation to the system: M0+18
• Initial positioning and monitoring of the move ments of the organs in relation to the patient: M0+36

X-1-4
Project 4: On-line PET imaging

Problem
Imaging using positron emission tomography (PET) is a technique based on the detection of two photons emitted at 180° by annihilation of a positron in matter. In light ion beam hadrontherapy, the detection of the positron emitting isotopes (produced by fragmentation of the carbon ions in living matter), makes it possible to monitor their path and thus determine the dose distribution [77]. This requires the development of an "on-line" PET system with a geometry adapted to being positioned around the patient during the treatment and consisting of high efficiency, high resolution detectors.

Scientific objectives

1. To simulate the fragmentation phenomena and the PET images obtained by such a system.
2. To adapt new technologies developed for the new generation of micro-PET
3. To perform experiments on phantoms and on animals
4. To design and build a prototype

Socio-economic spin-offs
Building such a prototype will require the use of the following technologies: new crystals (LSO/LuAP), new photodetectors (MaPMT, APD), low-noise high-speed electronics and reconstruction methods. This is a technological advance which could be directly transferred to the manufacturers of medical imaging and clinical systems. In view of the very high demand for the installation of PET systems in hospital environments for oncological applications (whole-body FDG PET examination), it is estimated that more than 200 machines will be installed in France over the next five years.

Laboratories currently involved
CERMEP GIE (CNRS, INSERM, HCL, UCBL), LPCML (UMR 5620 CNRS-UCBL), IPNL (UMR 5822 UCBL-CNRS)

Existing or planned collaboration
Crystal Clear Collaboration (CERN)
LETI (CEA) Grenoble

Programme
• State of the art (March 2002)
• Simulations and construction of a micro-PET measurement bench scan (June 2002)
• Design of a hadronPET (early 2003)
• Construction of a prototype microPET (late 2003)
• Construction of a hadronPET

X-2
Conformal radiotherapy
"Conformal" mode treatment, irrespective of the type of irradiation used, requires a number of stages:

- Control of the movements of the patient by manufacturing a personalised immobilisation device that is reliable and, if necessary, taking into account or controlling the movements of the internal organs of the patient (in particular, respiration)
- Acquisition of anatomical data (volume of tumour and healthy tissue) by three-dimensional (3-D) imaging, in practice, a "dosimetry" scan carried out in the position in which the patient will be treated.
- Definition by the physician, using 3-D imaging of the tumour target volume(s) to be irradiated ("anatomoclinical target volume(s)"), and the surrounding healthy tissue. Additional imaging, MRI (Magnetic Resonance Imaging) and PET scan may be of great assistance in improving precision. These additional images, which can be "merged" with the images provided by the scanner, make it possible to avoid irradiating a healthy organ unnecessarily and/or underestimating the volume of the tumour to be treated.
- Prescription by the physician of the doses of irradiation to be given for each anatomical target volume, and determination of the maximum dose and/or the maximum volume permitted for each type of healthy tissue or organ, to limit the risk of acute toxicity and of sequelae.
- The physicist and the physician taking a number of uncertainties into account to draw up the treatment plan (or "planimetry"). These uncertainties may be connected with the difficulties of "repositioning" the patient identically for each irradiation session, and with the movements of the internal organs, or perhaps, with the modification of the tumour target volumes and organs at risk during the treatment. These uncertainties are directly dependent on the quality of the immobilisation device used for the patient, the possibility of controlling or taking into account (modelling) the movements of the internal organs, and also the quality of the imaging used for control during the treatment (position of the patient in relation to the reference images, and position of the target volume if imaging of the internal organs is possible during radiotherapy). The uncertainty connected with the technique itself must be minimised. All the uncertainties must lead to the addition of a "safety margin" around the anatomical target volume, defining the "projected target volume".
- Carrying out the planimetry which must specify the best radiotherapy methods, and in particular the incidence of the radiotherapy beams and the distribution of the doses for each beam, in order to conform as closely as possible to the shape of the target volume, and achieve the objectives of minimum and maximum doses to be delivered to the tumour and to the organs at risk. The calculated risk of acute toxicity or sequelae connected with the irradiation of healthy tissue is the main factor limiting giving a high dose in the tumour.

Monitoring the irradiation. Only with carbon ion hadrontherapy can the doses actually deposited be monitored, by displaying the gamma particles produced by the destruction of the positrons emitted by carbon 10 and 11 ions resulting from the fragmentation of carbon 12.

X-3
Staff costs

Years	Total staff cost (technical and medical team) (k€)	Cost of technical team (k€)	Total cost of medical team (k€) (cf detail opposite)	Cost of medical team (kE) Type	Total	Production	Research	Teaching
				Physicians	53	0	53	0
				Physicists	143	0	143	0
				Dosimetrists	0	0	0	0
				Porters	0	0	0	0
				Nurses	0	0	0	0
				Reception	0	0	0	0
				Secret. Admin.	0	0	0	0
				Operators	0	0	0	0
				Nurses	0	0	0	0
0	684	487	197	Total	197	0	197	0
				Physicians	427	85	256	85
				Porters	61	61	0	0
				Nurses	38	38	0	0
				Reception	30	30	0	0
				Secret. Admin.	61	61	0	0
				Physicians	430	86	258	86
				Dosimetrists	78	31	31	16
				Operators	311	249	47	16
				Nurses	38	38	0	0
1	2 305	831	1474	Total	1474	680	592	202
				Physicians	640	256	256	128
				Porters	61	61	0	0
				Nurses	38	38	0	0
				Reception	30	30	0	0
				Secret. Admin.	61	61	0	0
				Physicians	573	229	229	115
				Dosimetrists	78	47	23	8
				Operators	389	311	58	19
				Nurses	38	23	8	8
2	3029	1121	1908	Total	1908	1056	574	278
				Physicians	1281	640	384	256
				Porters	61	61	0	0
				Nurses	114	114	0	0
				Reception	91	91	0	0
				Secret. Admin.	152	152	0	0
				Physicians	645	322	193	129
				Dosimetrists	155	124	23	8
				Operators	739	591	74	74
				Nurses	114	114	0	0
3	4474	1121	3353	Total	3353	2212	675	467

The staff for year 4 and subsequent years is the same as that for year 3.

• XI •

Glossary

ARMD	Age-related macular degeneration
Bolus	Tissue-equivalent material placed in contact with the irradiated area to provide, with the beams, an increase in the dose to the skin or a reduction of the beam. With electron beams, boluses are generally used to correct surface irregularities or to give the depth of the dose distribution a shape adapted to the anatomical structures to be protected or irradiated.
Bragg's peak	The dose distribution in depth of heavy charged particles is characterised by the existence of a plateau and a very narrow peak called Bragg's peak at the end of the range. The dose delivered to the tissue increases sharply at the apex of Bragg's peak.
Cell survival	Number of cells remaining alive after the action of radiation in relation to the number of initial cells in the population. By irradiating several identical cell populations with different doses, *survival curves* can be obtained.
Cobalt equivalent relative dose	The unit is the GyE (cobalt equivalent gray).
Concomitant	Carried out at the same time. For example, chemotherapy concomitant with radiotherapy: the chemotherapy is carried out on the same day as a radiotherapy session.
CTV: Clinical Target Volume	This volume includes the gross tumour volume (GTV) and the tissue surrounding the tumour which may be the seat of microscopic tumour proliferation and the neighbouring lymphatic drainage areas. This may result in a number of CTV. It is a purely anatomical concept which is independent of the treatment plan. It is this volume that must receive a sufficiently large dose to achieve the aim of the radiotherapy.
Dose (physical dose)	The physical dose is the amount of energy deposited by ionising radiation in a mass of material. The unit, *the gray* (Gy), corresponds to an absorbed energy of 1 joule per kilogram.
Dose rate	Quantity of dose expressed in grays deposited in tissue per unit of time. It is measured in Gy/min.

Equivalent biological dose	Physical dose delivered corrected by a biological effectiveness factor.
Fluence	The fluence of particles at a point is the quotient of the total number of particles which cross the elementary sphere centred on this point, by the area of the diametric cross-section. The unit is the cm^{-2}.
Fractionation	In radiotherapy the needed dose is delivered during several fractions to preserve the healthy tissues.
Fragmentation	Nuclear production reaction, by loss of one or more nucleons, from nuclei close to the incident nucleus with a wide distribution of energy and mass.
Gantry	Rotating isocentric device of radiotherapy equipment.
Gating	Synchronisation system for the operation or stopping of irradiation according to the respiratory or cardiac cycle.
Grade I toxicity	Does not require any treatment.
Grade II toxicity	Requires simple medical treatment.
Grade III toxicity	Severe toxicity with necrosis of tissue, jeopardizing the vital prognosis.
Grade IV toxicity	Requires the stopping of treatment and/or surgical treatment.
GTV: Gross Tumour Volume	Corresponds to the volume of the tumour which is clinically palpable or visible using current imaging methods.
Hadron	Heavy particle such as a proton, a neutron or an ion.
Hypoxia	Most cancers contain cells with deficient oxygenation (hypoxic cells). This hypoxia causes radioresistance (failure of radiotherapy) for low LET radiation.
Irradiated volume	Volume which receives a dose considered as being significant with respect to the tolerance of the healthy tissue.
Isocentre	For irradiation equipment with a rotating axis, centre of the smallest envelope sphere generated by the rotation of the axis of the beam around the axis of rotation of the equipment. For X and gamma radiation: point at which the axes of the beams meet.

Linear Energy Transfer (LET)	Energy deposited by the projectile per unit length of its trajectory expressed in KeV/mm.
Local control	Disappearance of the primary lesion during examinations after irradiation, and local absence of recurrence. The local control rate is the number of patients with local control expressed as a percentage of the number of patients treated.
Loi Huriet	Law governing clinical research in France. It places an obligation on the doctor to explain the aims and methods of the research to the patient and to obtain the patient's written consent.
Macula	Posterior area of the retina, 3 mm in diameter, which gives precise vision.
Multileaf collimator	A collimator is a device for delimiting the radiation beam. It generally consists of two pairs of jaws opposite one another delimiting beams to a square or rectangular cross-section. The movement of the jaws opposite one another in pairs may be symmetrical or asymmetrical in relation to the axis of the collimator. Multileaf collimators have jaws which are subdivided into independent leaves, enabling the direct creation of complex-shaped fields.
Oxygen effect	Oxygen increases the effects of ionising radiation on living matter. The lower the LET of the particle, the more marked this physical effect.
Oxygen Enhancement Ratio (OER)	This coefficient quantifies the *oxygen* effect. It is the ratio of doses with or without oxygen required to obtain the same biological effect.
Penumbra	Region, at the edge of the irradiation beam, in which the dose changes rapidly according to the distance to the axis of the beam. It is currently defined by the distance on a dose profile separating the points located at 20% and 80% of the dose respectively on the axis at a given depth in the medium.
Phantom	In radiotherapy, a phantom is an object which has similar properties to human tissue. It is frequently used in procedures for measurement of irradiation.

Phase I clinical trials	Clinical trial planned to evaluate a new therapeutic method in humans, in terms of safety and tolerable dose (chemotherapy, radiotherapy, etc). These trials are used in particular to determine the pharmacokinetic properties (metabolism, absorption, elimination and preferred method of administration) of new drugs. They are based on a limited number of people. As with all clinical trials, they are governed by the French Loi Huriet.
Phase II clinical trials	This is a clinical trial planned to evaluate the effectiveness (local control rates, survival, etc) of drugs, devices or diagnostic techniques, for therapy or prophylaxis (Loi Huriet).
Phase III clinical trials	Clinical trial which randomly compares the "new" treatment with the best existing treatment (reference treatment). It is the best "scientific" way of proving (or disproving) an increase in effectiveness (Loi Huriet). These trials require a large number of patients (more than 200).
Phase IV clinical trials	These are trials for monitoring drugs, devices or diagnostic techniques, for therapy or prophylaxis, which have been approved for general sale (marketing) following phase I, II and III clinical trials. These trials are often carried out to obtain additional information on the safety and effectiveness of a product.
Positron (e^+ or β^+)	Antiparticle of the same mass as the electron but with an opposite electrical charge and magnetic moment.
Positron emission tomography (PET)	There are some isotopes (11C, 15O, 13N) which have a short half life and which emit positrons. During the annihilation of the positrons two gamma photons are emitted simultaneously 180° from one another. From that point, the simultaneous use of a large number of detectors positioned in a ring around the patient (positron camera) enables coincidence detection of the arrival of the two photons and location of where they came from.
PTV: Planning Target Volume	The planning target volume is a geometric concept which is used to define the sizes of the beams and an appropriate treatment plan. This volume is obtained by adding a safety margin to the CTVs so that they receive the dose prescribed by the radiotherapist. It is the overall volume within which the CTV may move, influenced by the following factors: the physiological movements of the patient, the involuntary movements of the patient during the session and non-reproducibility of the positioning.

Randomised	The therapeutic method (new treatment being studied and "clinical" reference treatment) is decided randomly. Randomisation reduces the risk of error (differences between the two groups of patients receiving the new treatment and the reference treatment) in the interpretation of the trial results (phase III trial).
Rasterscanning	This technique is used to scan the target section by section using a thin pencil-beam.
Relative biological effectiveness (RBE)	This is the relationship of the dose of a reference radiation (X-rays, 60Co gamma radiation) to the physical dose of the radiation in question producing the same biological effect.
Sequential	Which controls an ordered series of operations. For example sequential chemotherapy and radiotherapy: the chemotherapy is administered first (over a few weeks or months) and then the radiotherapy.
Spread	Total duration (in days) of the radiotherapy.
Spread Out Bragg's Peak (SOBP)	Bragg's peak can be spread out with a high degree of uniformity of dose to cover the target volume. The technique consists of superimposing several single Bragg peaks using different beam energies.
Stages of cancer. TNM classification **T: Tumour** **N: Node** **M: Metastases**	The TNM classification provides a system for describing the extent of the cancer. T refers to the primary tumour, N refers to lymphatic nodes and M refers to the presence or absence or metastases distant from the primary tumour.
Stenosis	Narrowing of a canal or an orifice.
Synchrotron	Ring-shaped accelerator into which particles generally coming from a linear accelerator are injected. The magnetic field and the frequency of the acceleration voltage are increased simultaneously so that the orbit remains at a constant radius during the acceleration. Very high energies can be achieved and variable energies and intensities obtained at each pulse.

Treated volume	Volume contained in the isodose area specified by the radiotherapist corresponding to the minimum dose level which will enable the aim of the treatment to be achieved. Under ideal conditions it corresponds to the projected target volume.
Voxel scanning	Irradiation technique applied to the volume of the tumour similar to pixel scanning applied to an area.

• XII •

Acronyms and abbreviations

ANVAR	*Agence Nationale pour la Valorisation de la Recherche* State Technologie Transfer Agency
APD	*Avant Projet Détaillé* Detailed Preliminary Design
APS	*Avant Projet Simplifié* Simplified Preliminary Design
ARH	*Agence Régionale de l'Hospitalisation* Regional Hospitalization Agency
CCTP	*Cahier des Clauses Techniques Particulières* Special Technical Specifications
CEA	*Commissariat à l'Energie Atomique* Atomic Energy Agency
CERMEP	*Centre d'Exploration et de Recherche Médicales par Emission de Positons* Positron Emission Medical Investigation and Research Centre
CERN	*Centre Européen de Recherche Nucléaire* European Organization for Nuclear Research
CHU	*Centre Hospitalier Universitaire* University hospital
CLB	*Centre Léon Bérard*
CNA	Centro Nazionale di Adroterapia Italian hadrontherapy project
CNRS	*Centre National de la Recherche Scientifique* National Scientific Research Centre
COURLY	*Communauté Urbaine de Lyon* Lyon Metropolitan Authority
CREATIS	*Centre de Recherche et d'Applications en traitement de l'Image et du Signal* Research and Applications Centre for Image and Signal Processing
DESY	Deutsche Synchrotron
DRR	Digitally Reconstructed Radiography
DSM	*Direction des Sciences de la Matière* (CEA) Material Sciences Department
DSP	Digital Signal Processor
DSV	*Direction des Sciences du Vivant* (CEA) Life Sciences Department
ENLIGHT	European Network for Light Ions Therapy
EORTC	European Organisation for Research Treatment of Cancer
ESTRO	European Society of Therapeutic Radiation Oncology
FIMHO	*Fonds d'Investissement pour la Modernisation des Hôpitaux* Hospital modernization investment
GIE	*Groupement d'Intérêts Economiques* Economic Interest Grouping
GSI	Gesellschaft für Schwerionenforschung Society for heavy ion research
HCL	*Hospices Civils de Lyon* Lyon civil hospices
HICAT	Heavy Ion Cancer Therapy Facility
HIMAC	Heavy Ion Medical Accelerator of Chiba
IARC	International Agency for Research on Cancer
IN2P3	*Institut National de Physique Nucléaire et de Physique des Particules* National Institute for nuclear and particle physics
INRIA	*Institut National de Recherche en Informatique et Automatisme* National institute for research in computer science and control
INSERM	*Institut National de la Santé Et de la Recherche Médicale* National Institute for health and medical research
IPNL	*Institut de Physique Nucléaire de Lyon* Lyon nuclear physics institute
LASS	*Laboratoire d'Analyse des Systèmes de Santé* Health systems analysis laboratory
LBNL	Lawrence Berkeley National Laboratory
LET	Linear Energy Transfer
LIGIM	*Laboratoire d'Informatique Graphique Image et Modélisation* Computer Science Graphics Imaging and Modeling Laboratory
MRI	Magnetic Resonance Imaging
NIRS	National Institute of Radiological Sciences
ONDAM	*Objectif National de Dépenses en Assurance Maladie* National objective for health insurance expenditure
PET	Positron Emission Tomography
PIMMS	Proton Ion Medical Machine Study
RBE	Relative Biological Effectiveness

SFRO	*Société Française de Radiothérapie Oncologique* French society of oncological radiotherapy
TERA	Fondazione per Adroterapia Oncologica Foundation for oncological hadrontherapy
UCBL	*Université Claude Bernard Lyon 1*
uma	*Unité de masse atomique* Unit of atomic mass
VME	Data acquisition bus standard

• XIII •

Figures and tables
XIII-1
Figures

XIII - 2
Tables

• XIV •

References

[1] Gerard JP, Roy P, Cucherat M. *Local control of the primary tumor. Necessary step in control of cancer. Cancer Radiother.* 1998 Dec;2(6):668-71

[2] Suit HD. *Local control and patient survival.* Int J Radiat Oncol Biol Phys 1992;23:653-60

[3] Arriagada R, Cosset JM, le Chevalier T, Tubiana M. *The value of adjunctive radiotherapy when chemotherapy is the major curative method.* Int J Radiat Oncol Biol Phys. 1990 Nov;19(5):1279-84

[4] *Symposium sur l'hadronthérapie.* Hôtel de ville de Lyon. Mars 2000. LYCEN report 00-112

[5] Bey P, Gerard JP. *Practical determination of volume and doses in conformal radiotherapy. Cancer Radiotherapy.* 1998;2:615-8

[6] Carrie C, Ginestet C. *New techniques and methods in transcutaneous radiotherapy.* Bull Cancer. 2001;88:59-65

[7] Pommier P, Ginestet C, Carrie C. *Is conformal radiotherapy a progress ? What are its difficulties and limits ?* Cancer Radiother. 2001;5 (suppl 1): 57-67

[8] Malet C, Ginestet C, Hall K, Lafay F, Sunyach M, Carrie C. *A study of dose delivery in small segments.* Int J Radiat Oncol Biol Phys. 2000;48:535-9

[9] Ginestet C, Malet C, Cohen A, Lafay F, Carrie C. Impact of tissues heterogeneities on monitor units calculation and ICRU dosepoint: analysis of 30 cases of prostate cancer treated with 18-MV photons after three-dimensional planning. Int J Radiat Oncol Biol Phys. 2000;48:529-34

[10] Pollack A, Zagars GK, Smith LG, Lee JJ, von Eschenbach AC, Antolak JA, Starkschall G, Rosen I. *Preliminary results of a randomized radiotherapy dose-escalation study comparing70 Gy with 78 Gy for prostate cancer.* J Clin Oncol. 2000;18:3904-11

[11] Bey P, Carrie C, Beckendorf V, Ginestet C, Aletti P, Madelis G, Luporsi E, Pommier P, Cowen D, Gonzague-Casabianca L, Simonian-Sauve M, Maingon P, Naudy S, Lagrange J, Marcie S. Dose *escalation with 3D-CRT in prostate cancer: French study of dose escalation with conformal 3D radiotherapy in prostate cancer.* Preliminary results. Int J Radiat Oncol Biol Phys 2000; 48:513-7

[12] Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M. *Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin.* N Engl J Med. 1997;337:295-300

[13] Giraud P, Antoine M, Larrouy A, Milleron B, Callard P, De Rycke Y, CaretteMF, Rosenwald JC, Cosset JM, Housset M, Touboul E. *Evaluation of microscopic tumor extension in non-small-cell lung cancer forthree-dimensional conformal radiotherapy planning.* Int J Radiat Oncol Biol Phys 2000; 48:1015-24

[14] Giraud P, Grahek D, Montravers F, Carette MF, Deniaud-Alexandre E, Julia F,Rosenwald JC, Cosset JM, Talbot JN, Housset M, Touboul E. CT and 18F-*deoxyglucose (FDG) image fusion for optimization of conformalradiotherapy of lung cancers.* Int J Radiat Oncol Biol Phys 2001;49:1249-57

[15] Troccaz J, Vassal P, Giraud JY, le Verre C, Artignan X, Bolla M. *Image fusion methods for the repositioning of the patient in radiotherapy.* Cancer Radiother 2000;4 (Suppl 1):31s-35s

[16] Giraud P, De Rycke Y, Dubray B, Helfre S, Voican D, Guo L, Rosenwald JC, Keraudy K, Housset M, Touboul E, Cosset JM. *Conformal radiotherapy (CRT) planning for lung cancer: analysis of intra*thoracic *organ motion during extreme phases of breathing.* Int J Radiat Oncol Biol Phys 2001;51:1081-92

[17] Sunyach MP, Falchero L, Pommier P, Perol M, Arpin D, Vincent M, Boutry D,Rebatu P, Ginestet C, Martel-Lafay I, Perol D, Carrie C. *Prospective evaluation of early lung toxicity following three-dimensional conformal radiation therapy in non-small-cell lung cancer: preliminary results.*Int J Radiat Oncol Biol Phys. 2000;48:459-63

[18] Claude L, Falchero L, Arpin D, Perol D, Vincent M, Cordier JF, Guerin JC, Carrie C. Can we predict pulmonary complications in lung cancer treated with conformal radiotherapy (3DCRT): prospective of Normal Tissue Dose Volume Histograms (DVHs) and pulmonary function relations. Int J Radiat Oncol Biol Phys. 2001;51(suppl 1):87

[19] Rosenzweig KE, Sim SE, Mychalczak B, Braban LE, Schindelheim R, Leibel SA. *Elective nodal irradiation in the treatment of non-small-cell lung cancer with three-dimensional conformal radiation* therapy.Int J Radiat Oncol Biol Phys. 2001; 50:681-5

[20] Hayman JA, Martel MK, Ten Haken RK, Normolle DP, Todd RF 3rd, Littles JF, Sullivan MA, Possert PW, Turrisi AT, Lichter AS. *Dose escalation in non-small-cell lung cancer using three-dimensional conformalradiation therapy: update of a phase i trial.* J Clin Oncol. 200; 19:127-36

[21] Rosenzweig KE, Mychalczak B, Fuks Z, Hanley J, Burman C, Ling CC, ArmstrongJ, Ginsberg R, Kris MG, Raben A, Leibel S. *Final report of the 70.2-Gy and 75.6-Gy dose levels of a phase I dose escalation study using three-dimensional conformal radiotherapy in the treatment of inoperable non-small cell lung cancer.* Cancer J. 2000; 6:82-7

[22] Pommier P, Lapeyre M, Ginestet C, Buchheit I, Sunyach MP, Chapet O, Montbarbon X, Marchal C, Aletti P, Carrie C, Bey P. *Conformal radiotherapy in cancer of the upper aerodigestive tract.* Cancer. Radiother. 1999; 3:414-24

[23] Pommier P, Ginestet C, Sunyach M, Zrounba P, Poupart M, Ceruse P, Ciupea C, Carrie C, Montbarbon X. *Conformal radiotherapy for paranasal sinus and nasal cavity tumors:three-dimensional treatment planning and preliminary results in 40 patients.* Int J Radiat Oncol Biol Phys. 2000 Sep 1;48(2):485-93

[24] Wolden SL, Zelefsky MJ, Hunt MA, Rosenzweig KE, Chong LM, Kraus DH, PfisterDG, Leibel SA. *Failure of a 3D conformal boost to improve radiotherapy for nasopharyngealcarcinoma.* Int J Radiat Oncol Biol Phys 200; 49:1229-34

[25] Tubiana M, Eschwege F. *Conformal radiotherapy and intensity-modulated radiotherapy: clinical data.* Acta Oncol 2000; 39:555-67

[26] Chao KS, Majhail N, Huang C, Simpson JR, Perez CA, Haughey B, Spector G. *Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control in patients with oropharyngeal carcinoma: a comparison with conventional techniques. Radiother* Oncol 2001;61:275-80

[27] Hunt MA, Zelefsky MJ, Wolden S, Chui CS, LoSasso T, Rosenzweig K, Chong L,Spirou SV, Fromme L, Lumley M, Amols HA, Ling CC, Leibel SA. *Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer.* Int J Radiat Oncol Biol Phys 2001;49:623-32

[28] Sultanem K, Shu HK, Xia P, Akazawa C, Quivey JM, Verhey LJ, Fu KK. *Three-dimensional intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: the University of California-San Francisco experience.* Int J Radiat Oncol Biol Phys. 2000;48:711-22

[29] Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC, Reuter VE,Venkatraman ES, Leibel SA. *High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer.* J Urol 2001; 166:876-81

[30] *Programme de soutien aux innovations diagnostiques et thérapeutiques coûteuses.* 2001. Ministère de la santé et Direction des hôpitaux

[31] *Usage thérapeutique des cyclotrons en cancérologie: évaluation clinique et économique.* Agence Nationale pour le Développement de l'Evaluation Médicale, mars 1995

[32] Courdi A, Caujolle JP, Grange JD, Diallo-Rosier L, Sahel J, Bacin F, Zur C, Gastaud P, Iborra-Brassart N, Herault J, Chauvel P. *Results of proton therapy of uveal melanomas treated in Nice.* Int J Radiat Oncol Biol Phys 1999; 45:5-11

[33] Noël G, Habrand JL, Mammar H et al. *Combination of photon and proton radiation therapy for chordomas and chondrosarcomas of the skull base: the Centre de Protontherapy d'Orsay experience.* Int J Radiat Oncol Biol Phys 2001; 51:392-8

[34] Tsujii H, Tsuji H, Inada T, Maruhashi A, Hayakawa Y, Takada Y, Tada J,Fukumoto S, Tatuzaki H, Ohara K, et al. *Clinical results of fractionated proton therapy.* Int J Radiat Oncol Biol Phys. 1993; 25:49-60

[35] Orecchia R, Zurlo A, Loasses A, Krengli M, Tosi G, Zurrida S, Zucali P,Veronesi U. *Particle beam therapy (hadrontherapy): basis for interest and clinical experience.* Eur J Cancer. 1998 Mar;34(4):459-68

[36] Cella L, Lomax A, Miralbell R. *Potential role of intensity modulated proton beams in prostate cancer radiotherapy.* Int J Radiat Oncol Biol Phys 2001;49:217-23

[37] Bush DA, Slater JD, Bonnet R, Cheek GA, Dunbar RD, Moyers M, Slater JM. *Proton-beam radiotherapy for early-stage lung cancer.* Chest 1999;116:1313-9

[38] Laramore GE, Krall JM, Griffin TW, Duncan W, Richter MP, Saroja KR, Maor MH, Davis LW. *Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy OncologyGroup. Medical Research Council.* Int J Radiat Oncol Biol Phys 1993;27:235-40

[39] Pickering DG, Stewart JS, Rampling R, Errington RD, Stamp G, Chia Y. *Fast neutron therapy for soft tissue sarcoma.* Int J Radiat Oncol Biol Phys. 1987;13:1489-95

[40] Russell KJ, Caplan RJ, Laramore GE, Burnison CM, Maor MH, Taylor ME, Zink S, Davis LW, Griffin TW. *Photon versus fast neutron external beam radiotherapy in the treatment of locally advanced prostate cancer: results of a randomized prospective trial.* Int J Radiat Oncol Biol Phys. 1994;28:47-54

[41] Maor MH, Errington RD, Caplan RJ, Griffin TW, laramore GE, Parker RG,Burnison M, Stetz J, Zink S, Davis LW, et al. *Fast-neutron therapy in advanced head and neck cancer: a collaborative international randomized trial.* Int J Radiat Oncol Biol Phys 1995;32:599-604

[42] Koh WJ, Krall JM, Peters LJ, Maor MH, Laramore GE, Burnison CM, Davis LW,Zink S, Griffin TW. *Neutron vs. photon radiation therapy for inoperable regional non-small cell lung cancer: results of a multicenter randomized trial.* Int J Radiat Oncol Biol Phys 1993;27:499-505

[43] Thomas FJ, Krall J, Hendrickson F, Griffin TW, Saxton JP, Parker RG, DavisLW. *Evaluation of neutron irradiation of pancreatic cancer. Results of a randomized Radiation Therapy Oncology Group clinical trial.* Am J Clin Oncol. 1989;12:283-9

[44] Laramore GE, Diener-West M, Griffin TW, Nelson JS, Griem ML, Thomas FJ,Hendrickson FR, Griffin BR, Myrianthopoulos LC, Saxton J. *Randomized neutron dose searching study for malignant gliomas of the brain: results of an RTOG study. Radiation Therapy Oncology Group.* Int J Radiat Oncol Biol Phys. 1988;14:1093-102

[45] Hideghéty K, Sauerwein W, Haselsberger K et al. Strahlenther Onkol,175:111-4, 1999

[46] Kaplan ID, Castro JR, Phillips TL. *Helium charged particle radiotherapy for meningioma: experience at UCLBL.University of California Lawrence Berkeley Laboratory.* Int J Radiat Oncol Biol Phys 1994;28:257-61

[47] Kraft G, Scholz M. *On the parameterization of the biological effect in a mixed radiation field.* Adv Space Res, 14:997-1004,1994

[48] Kramer M, Kraft G. *Track structure and DNA damage.* Adv Space Res, 14:151-9, 1994

[49] Scholz M, Kraft G. *Track structure and the calculation of biological effects of heavy charged particles.* Adv Space Res, 18:5-14, 1996

[50] Kanai T et al, Rad Res, 147:78-85, 1997.(HIMAC, NIRS, Chiba, Japan)

[51] Tubiana M et coll. *Radiobiologie.* Editions Hermann 1986

[52] Barendsen GW. *Radiobiology of neutrons.* Int J Radiat Oncol Biol Phys, 8:2103-7, 1982

[53] Castro JR. *Results of heavy ion radiotherapy.* Radiat Environ Biophys,34:45-8, 1995

[54] Nakano T, Suzuki M, Abe A, Suzuki Y, Morita S, Mizoe J, Sato S, Miyamoto T, Kamada T, Kato H, Tsujii H. *The phase I/II clinical study of carbon ion therapy for cancer of the uterine cervix.* Cancer J Sci Am, 5: 362-9, 1999

[55] Castro JR, Linstadt DE, Bahary JP, Petti PL, Daftari I, Collier JM, Gutin PH, Gauger G, Phillips TL. *Experience in charged particle irradiation of tumors of the skull base:1977-1992.* Int J Radiat Oncol Biol Phys 1994;29:647-55

[56] Schoenthaler R, Castro JR, Petti PL, Baken-Brown K, Phillips TL. *Charged particle irradiation of sacral chordoma.* Int J Radiat Oncol Biol Phys 1993;26:291-8

[57] Schoenthaler R, Castro JR, Halberg FE, Phillips TL. *Definitive postoperative irradiation of bile duct carcinoma with chargedparticles and/or photons.* Int J Radiat Oncol Biol Phys 1993;27:75-82

[58] Tsujii H, Morita S, Miyamoto T, Mizoe J, Nakano T, Kamada T, Kato H. *The current status and perspective of heavy-ion therapy.* ICRO/ÖGRO6 6th Interational Meeting on Progress in Radio-Oncoly, 1998:709-21

[59] Tsujii H. *Current status of hadrontherapy with carbon ion beams.* Eur J Cancer 2001;37(suppl. 6):251

[60] Kamada T, Tsujii H, Tsuji H, Yanagi T, Mizoe J, Miyamoto T, Morita S, Kato H, Yamada S, Tateishi A. *A phase I/II clinical trial of Carbon-ion therapy for patients with bone and soft tissue sarcomas not suited for surgical resection.* Eur J Cancer 2001;37(suppl. 6):84

[61] Tsujii H. *Experiences of conformal radiotherapy with carbon ion beams. Advanced in 3D CRT/IMRT: what the Millennium holds.* The 3rd Takahashi Memorial international Workshop, 2001

[62] Debus J, Haberer T, Schulz-Ertner D, Jakel O, Wenz F, Enghardt W, Schlegel W, Kraft G, Wannenmacher M. *Carbon ion irradiation of skull base tumors at GSI. First clinical results and future perspectives.* Strahlenther Onkol 2000;176:211-6

[63] Schulz-Ertner D, Haberer T, Jakel O, Thilmann C, Kramer M, Enghardt W, Kraft G, Wannenmacher M, Debus J. *Radiotherapy for chordomas and low-grade chondrosarcomas of the skull base with carbon ions.* Int J Radiat Oncol Biol Phys. 2002;53:36-42

[64] Bartelink H. *From translational research to improved local control and survival:* the Gilbert Fletcher Award Lecture, Lugano, March 2000. Int J Radiat Oncol Biol Phys. 2001;49(2):311-8 Hideghéty K, Sauerwein W, Haselsberger K et al. Strahlenther Onkol,175:111-4, 1999

[65] Ferlay J, Bray F, Sankila R, Parkin DM. EUCAN 1999. *Cancer Incidence, Mortality and Prevalence in the European Union.* IARC Press, Lyon 1999

[66] Amaldi U, Larsson B. Hadrontherapy in Oncology. Proceedings of the first international symposium on hadrontherapy, ELSEVIER,1994

[67] Amaldi U et al. *The National Centre for Oncologocal Hadrontherapy at Mirasole.* Fondation TERA, INFN, Frascati, 1997 (ISBN 88-86409-29-X)

[68] Orecchia R. *What is the clinical and research validity of Hadrontherapy with beams of protons and ions.* TERA 2001/8 GEN 32

[69] De Vita VT, Hellmann S, Rosenberg SA (eds). Cancer: *Principles and practise of oncology.* Philadelphia:J.B. Lippincott Company, 1993

[70] Perez CA, Brady LW (eds). *Principles and practice of Radiation Oncology.* Philadelphia:J.B. Lippincott Company, 1992

[71] Gunderson LL, Tepper JE (eds). *Clinical Radiation Oncology.* Philadelphia:Churchill Livingstone, 2000

[72] Rakotomalala H. *Modélisation de la distribution de dose en protonthérapie par superposition de faisceaux élémentaires.* Thèse de doctorat de l'université Paul Sabatier, spécialité:Physique radiologique et médicale. 20/12/2000

[73] Kramer M, Jakel O, Haberer T, Kraft G, Schardt D, Weber U. *Treatment planning for heavy ions radiotherapy: physical beam model and dose optimization.* Phys Med Biol 2000 nov., 45 (11) 3299-3317

[74] Gueulette J et al. *Protons RBE for early intestinal tolerance in mice after fractionated irradiation.* Radiotherapy and oncology 61 (2001) 177-184

[75] Amrani M, Jaillet F, Shariat B. *Deformable objects modelling and animation: application to organ's interactions simulation.* Journal for Geometry and Graphics, 4(2):181-188, 2000

[76] Amrani M, Crespin B and Shariat B. "*Skeletal Implicit Surface Reconstruction from Contours for Rigid-body Simulation*", Proceedings of the 2001 IEEE Conference on Information Visualization, London, UK, pages 723-728, July 2001

[77] *Proposal for a dedicated ion beam facility for cancer therapy.* Universitätklinik Heidelberg, Deutsches Krebsforschungzentrum Heidelberg, Gesellschaft für Schwerionenforschung Darmstadt (1998). Annexe D7

Notes

ETOILE Project:

European Light Ion Oncological Treatment Centre

VOLUME 2 :
Preliminary technical design

• Preface •

The Université Claude Bernard Lyon 1 took the initiative in 1999 to ask a number of physicians and physicists to draw up a specification for the creation of a Light Ion Hadrontherapy Centre. Under the auspices of this university and with the financial support of the local authorities and the Ministry for Research a preliminary design was undertaken corresponding to this specification. The technical part of this design was the subject of a research contract between the University (UCBL), the Commissariat à l'Energie Atomique (CEA-DSM) and the Centre National de la Recherche Scientifique (CNRS-IN2P3).

This report is thus the result of close collaboration between physicians (oncologists and radiotherapists) and medical physicists from Lyon and Grenoble University Hospitals and Regional Anticancer Centre Léon Bérard (Lyon), scientists (physicists, computer scientists and health economists, from the universities of Lyon and Grenoble) and engineers specializing in accelerators (CEA, IN2P3, CERN, GSI, TERA). Together they constitute a substantial multidisciplinary team capable of defining the structure and cost of the project, recently named ETOILE, and of initiating the research programmes necessary to perfect this innovative therapy.

This project has taken full account of the experimental work carried out in Japan and Germany. It is part of a coordinated European approach, with similar projects developed in Germany, Italy, Sweden and Austria. Clearly the result of the conjunction of the research and clinical worlds, its future will include being taken on by the national health system and the involvement of national and regional decision-makers.

This study:
• was set up under the project managership of the Université Claude Bernard Lyon 1 (UCBL), which initiated the project,
• involves physicians, medical physicists, scientists and engineers from: UCBL, Université Joseph Fourier Grenoble 1, the University Hospital (Hospices Civils de Lyon) in Lyon, the University Hospital in -Grenoble, the Regional AnticancerAnticancer Centre Léon Bérard in Lyon, the Orsay and Nice proton-therapy centres, CNRS, CEA, CERN, GSI (Darmstadt), TERA (Milan), ESRF (Grenoble) and GANIL (Caen),
• is the subject (for the technical part) of a research contract between UCBL, CNRS/IN2P3 and the CEA/DSM,
• has been funded initially by the Rhône-Alpes Region, the Metropolitan Authority of Lyon, ANVAR and UCBL, and then in the context of the "Hadrontherapy" budget of the current State-Regional Spending Plan (Ministry for Research, Rhône-Alpes Region and Metropolitan Authority of Lyon).

The following people have been involved in the preparation of this document

Steering committee
Jean Pierre Gérard (Regional Anticancer Centre A. Lacassagne, Nice) medical director of the project
Joseph Remillieux (UCBL/IPN Lyon) physics director of the project
Joël Rochat UCB Lyon (UCBL) project manager
François Dupont/Marcel Lieuvin (CNRS/IN2P3 department)
Yves Terrien (CEA/DSM department)

Medical study group
Jacques Balosso University Hospital, Grenoble
Michel Bolla University Hospital, Grenoble
Chantal Ginestet CLB Lyon
Jean-Yves Giraud University Hospital,Grenoble
Patrice Jalade University Hospital,Lyon
Alejandro Mazal Institut Curie Paris
Jean-Claude Rozenwald Institut Curie Paris
Pascal Pommier Regional Anticancer Centre, Lyon
Dominique Sappey-Marinier CERMEP/UCB Lyon

Technical study group
Jean-Marie De Conto CNRS/IN2P3 ISN Grenoble, technical project manager
Marcel Bajard CNRS/IN2P3 IPN Lyon, joint technical project manager
Rodolphe Antoni CEA/DEN/SAC/DSP/SPR Saclay
Patrick Ausset CNRS/IN2P3 IPN Orsay
Laurent Bourgois CEA/DEN/SAC/DSP/SPR Saclay
Jean Michel Buhour CNRS/IN2P3 IPN Orsay
Olivier Delferriere CEA /DSM/DAPNIA/SEA Saclay
Denis De Menezes CEA /DSM/DAPNIA/SEA Saclay
Michel Fruneau CNRS/IN2P3 ISN Grenoble
Jean François Gournay CEA /DSM/DAPNIA/SIG Saclay
Jean Luc Jannin CEA /DSM/DAPNIA/SEA Saclay
Jean Michel Lagniel CEA /DSM/DAPNIA/SEA Saclay
Bernard Launé CNRS/IN2P3 IPN Orsay
Alain Le Gendre CNRS Paris
François Méot CEA /DSM/DAPNIA/SEA Saclay
Nelly Rouvière CNRS/IN2P3 IPN Orsay
Armand Sinnana CEA /DSM/DAPNIA/SEA Saclay
Pascal Sortais CNRS/IN2P3 ISN Grenoble
André Tkatchenko CNRS/IN2P3 IPN Orsay

Scientific study group
Michael Beuve UCB Lyon/LIGIM
Flavien Brossard UCBL/IPN Lyon
Jean-Pierre Claveranne UJM Lyon/LASS
Yves Déclais CNRS/IN2P3 IPN Lyon
Albert Demeyer UCB Lyon/IPN Lyon
Florent Dupont UCB Lyon/LIGIM
Gérard Duru UCB Lyon/LASS
André Emsallem UCB Lyon/IPN Lyon
Fabien Feschet UCB Lyon/LASS
Fabrice Jaillet UCB Lyon/LIGIM
Guillaume Largeron UCB Lyon
Christophe Pascal UJM Lyon/LASS
Behzad Shariat UCB Lyon/LIGIM

Secretarial support
Jocelyne Charnay CNRS/IN2P3 IPN Lyon
Marie Louise Lombard CNRS/IN2P3 ISN Grenoble

Acknowledgements

Ministry for Research
Ministry of Employment and Solidarity
Ministry of Industry
Rhône-Alpes Region
Metropolitan Authority of Lyon
UCB Lyon chair
UJF Grenoble chair
Management of CNRS/IN2P3
Management of CEA/DSM
Management of CEA/DSM/DAPNIA
Management of IPN Lyon
Management of ISN Grenoble
Management of IPN Orsay
Management of Hospices Civils de Lyon
Management of CHU Grenoble
Management of Centre Léon Bérard Lyon
Management of Hôpital du Vinatier Bron
Management of CERN
Management of ANVAR Rhône-Alpes

As well as Messrs :
Tsujii (NIRS-Chiba)
Amaldi, Crescenti, Gramatica, Pullia, Rossi (TERA Foundation)
Eickhoff, Haberer, Henning, Kraft, Krause, Schlitt, Steiner (GSI)
Bryant, Détraz, Grüber, Hoffmann, Hübner, Kahle, Thivent (CERN)
Palanque (CEA)
Ferrand, Meyroneinc (CPO)
Bouteille, Hardy, Jacob, Magnien (ESRF)
Baron, Berthe, Petit, Rannou (GANIL)
Poizat (IPNLyon)
Mongereau (INSA Lyon)

Foreword

Successful treatment of cancerous tumours frequently involves irradiation. This is most often performed using X rays, but also, more rarely, using proton beams (proton-therapy) or neutron beams (neutrontherapy). One method, light ion hadrontherapy, has been tested in Japan and Germany for several years. This method, which requires heavy-duty equipment, has demonstrated the advantage of these ions, and in particular carbon ions, for the accurate treatment of deep-seated tumours which are inoperable and radioresistant.

The French ETOILE project: Espace de Traitement Oncologique par Ions Légers Européen (European Light Ion Oncological Treatment Centre) proposes to build a carbon ion hadrontherapy centre in the Rhône-Alpes region of France. This project is based on the promising clinical results obtained recently at Chiba in Japan and Darmstadt in Germany, following on from the pioneering work initially carried out at Berkeley in the USA. We are not the only organization with this aim, as a fairly similar development will be initiated shortly in Heidelberg, Germany, and projects at a similar stage as ours are in preparation in Milan, Stockholm and Vienna. The emergence in Europe of a number of projects collaborating with one another in a network is absolutely necessary for the clinical validation of treatment using carbon ions.

We are convinced that France has the resources to develop such a centre, which will be able to cure more than 500 of the 1000 patients treated each year (for whom existing treatments would have little effect). This will help to put France back in the market for heavy-duty equipment for medicine. This aim is economically viable in that the cost of treatment is lower than other cancer therapies currently in use.

The French project will be located in Lyon, in the Rhône-Alpes region. This decision is justified both by the strong initial commitment of the Claude Bernard and Joseph Fourier scientific and medical universities at Lyon and Grenoble respectively. In addition, Geneva the home of CERN where the study of a synchrotron (PIMMS) adapted to the medical requirements of hadrontherapy was carried out, is close. This project has been made possible by the tight collaboration between the French universities, the CEA (DSM) and the CNRS (IN2P3). Moreover, a European network (ENLIGHT) has recently been created to co-ordinate the essential medical and technical collaboration between the various European projects.

The multidisciplinary research programmes that have been undertaken around the ETOILE project are essential for the provision and control of treatment plans for patients. They ensure that all the clinicians, radiobiologists, medical physicists, physicists, engineers, computer scientists and economists work together. There is no doubt that if this project is a success, there will be considerable medical and economic spin-offs throughout the whole health sector, in particular in the fields of oncology, including radiotherapy, imaging and medical physics.

Contents of volume II

• I •
Introduction

Volume II of the ETOILE project concerns the preliminary technical design of the devices required to produce, select, accelerate, shape, transport to the treatment rooms, distribute and control the ion beams in the target volume to be treated in accordance with the requirements determined by the calculations of the treatment plan.

It presents a solution for their installation in a building on a site chosen as the reference and covers the various technical and medical areas necessary for the operation of a treatment centre.

The problems of safety are examined from the point of view of the patients, the staff and the environment.

Although they are covered in detail in volume I, the medical and technical performance specifications and a description of the site are repeated in this volume. This volume also contains a summary of the capital costs and the development programme with the associated resources.

I-1
Medical performance specifications

Projectiles	ions $^{12}C^{6+}$
Possibility of other projectiles	from protons to ^{16}O
Time for changeover between two types of particle	< 1 hour
Depth of penetration of ions (p, C)	2 to 27 cm in water
Maximum dimensions of the area of irradiation (perpendicular to the direction of the incident beam)	20 x 20 cm^2
Maximum continuous physical dose rate	2 Gy with a treatment time of one minute per litre
Distribution of the dose in the target volume (max I and E)	
Distal drop 100% - 30%	less than 3 mm
Lateral penumbra 80% - 20%	less than 2 mm
Lateral precision of the direction of the incident beam	2 mm at the target volume
Diameter of the beam at mid-height	variable from 4 to 10 mm
Spatial resolution of the field of irradiation	~ 2 mm
Angular rasterscanning of the beam	Yes
Distance between scanning magnets and isocentre of the tumour	> 3 m
Possibility of distributing very low doses	Yes
Possibility of several incident directions of the beam in one room	Yes
Safety of the patient:	
- rapid stopping time	200 μs
- uniformity of the dose in the target volume	tolerable deviation ± 2.5%
- precision of the dose delivered	± 2.5%
Irradiation techniques with the beam:	
Active: energy can be varied rapidly	Yes
intensity can be varied rapidly	Yes
position of "pencil" beam can be varied	Yes
Examine the possibility of also having passive irradiation	Yes
Number of rooms [1]	- 2 treatment rooms with horizontal beam - 1 treatment room with vertical beam (with the possibility of installing an additional horizontal beam)
Equipment in treatment rooms	- possibility of robot-controlled beds and/or chairs - 3 X-ray tubes for digital imaging, possibility of PET - marker systems
Rooms attached to each treatment room	1 pre-positioning room 1 irradiation control room
Number of simulation rooms with X-ray scanner	1 to 2
Number of patients per annum	50 to 100 in the first year, 200 to 500 in the second year, 500 to 1000 in the third year
Minimum dosimetry (measurements) just before the patient Per beam line	Ionization chambers - 2 for controlling the position and shape of the beam - 2 for controlling the dose - 1 for redundancy
Number of treatment planning rooms (planned dosimetry)	2 rooms with 3 consoles per room

[1] During this preliminary design the benefit of carrying out the preliminary investigation of a treatment room with rotating isocentric gantry has come to light.

Precision of the positioning of the patient in relation to the beam, with appropriate immobilization device	Head : 1 mm Body : 2 mm
Areas to be provided	Reception, management, administration, secretarial offices, waiting rooms, consulting rooms, anesthetics room, offices for: doctors, physicists, engineers, technical areas, maintenance, storage (including activated materials), diagnostics, library, archives, visitors, meeting rooms, toilets
Assumption for work with three treatment rooms	1000 patients routinely treated per annum after three years' operation 15 sessions on average per patient 220 days of treatments per annum

Table I-1: medical performance specifications

I-2
Technical specifications

Variable energy accelerator	Synchrotron
Sources	2 ion sources for carbon ions and protons (+ possibility of using other ions) ECRIS type (Electron Cyclotron Resonance Ion Source)
Ions delivered in the rooms	$^{12}C^{6+}$, $^{1}H^{1+}$
Final energies for 2 to 27 cm penetration in water	C: 85 – 400 MeV/uma p: 50 – 200 MeV
Variation of the energy and intensity	The variation of the energy requires rapid adjustments of the accelerator (around 1 second)
Variation of the penetration depth	In 1 mm steps if the penetration is less than 20 cm In 1.5 mm steps if the penetration is greater than 20 cm
Variation of the beam size (total width at mid-height)	4 to 10 mm spot with diameter adjustable by steps of 2 mm at the patient
Number of energy steps	255
Typical beam intensity for a physical dose rate of 2 Gy/min per litre Variations for each energy according to the treatment plan and the shape of the tumour	Maximum number of particles per spill at the patient : $^{12}C^{6+}$: $\sim 4 \times 10^{8}$ protons $\sim 1 \times 10^{10}$ typical values for active scanning (ref: PIMMS [7] in volume II) Imax/Imin intensity variation = 1000 Cycle duration: 1 to 10 seconds
Fluctuation of the position of the beam at the isocentre during the extraction cycle	Less than ± 15% of the diameter of the spot at mid-height
Rasterscanning of the beam in the treatment room	Horizontal and vertical scanning magnets
Parallax	Distance between scanning source and isocentre of the tumour greater than 3 m
Easily variable beam entry angles	Rotating isocentric gantry instead of the fixed vertical beam
Reproducibility of the dose delivered, its uniformity and its contours	Contamination of the beam less than 1% Precise on-line monitoring of the parameters of the beam On-line monitoring of the spectrum of the ion source
Fast stopping of the beam	Rapid deflector, in 200 ms Associated mechanical stopping of the beam

Table I-2: technical specifications

I-3
Reference site
The main characteristics of the site are as follows:

A location in an urban area surrounded by residential blocks of flats, private houses, hospitals and research centres, next to the Lyon ring road.

The location stands on 50 m of fluvioglacial alluvial rocks which are themselves on top of a thick layer of argillaceous molasse. Data concerning the hydrology of the site lead us to believe that it would be possible to draw off water for cooling the equipment of the centre (quantity less than 200 m^3 per hour) which would avoid the necessity for a system based on cooling towers.

The site is large enough to be able to accommodate additional buildings for new technical facilities and to house patients or research staff on a temporary basis.

• II •

Reasons for the choice of machine

First of all, the reasons which have led to the choice of a synchrotron (the main element of the facility) will be given. Then a detailed technical description will be given of each subsystem.

• Choice of a synchrotron

The synchrotron is the type of accelerator which best meets the specifications. It is needed to be able to treat tumours which have a complex shape, and which may be mobile, in a minimum amount of time. If half an hour per session is not to be exceeded, it is essential that the irradiation itself does not exceed 5 to 6 minutes.

The synchrotron meets the medical specifications and provides the required flexibility.

- Energy and intensity can be chosen at each spill of particles according to the depth to be reached in the tissue and the dose to be deposited in the tumour.

- For the treatment of mobile tumours, the spill may be triggered by a "gating" signal. The cycle may have a variable duration (1.4 to 10 seconds from spill to spill), and can thus adapt to the biological rhythm of the patient.

- For the treatment of tumours which are not connected, the spill can be interrupted within one cycle so that healthy tissue between the two separate parts of the tumour is not irradiated. This configuration is very common.

• Feasibility

The medical use of the synchrotron has been demonstrated in a large number of cases, for example in Germany, Japan and the United States. It has been adopted for all new-generation facilities devoted to the treatment of cancer using light ions, when the energies are around 400 MeV/amu (HICAT project in Heidelberg, CNA Italian project, Swedish project at the Karolinska Institute, Austrian Med-AUSTRON project).

• Advantages of the synchrotron

The reason for this choice will not be covered in detail here as it has already been widely covered in many technical studies carried out over the last 10 years and in many initiatives proposing a dedicated hospital-based facility [1] [2] [3] [4] [5] [6]. However the main arguments in favour of a synchrotron are:

- More suited to the acceleration of high energy ions,
- Possibility of precise variation of energy from one spill to the next,
- Rapid switching between different types of ion,
-Three-dimensional conformal irradiation of deep seated tumours,
- Ease of maintenance and access for repair,
- High level of reliability.

• Structure of the synchrotron

The design principle of an optical synchrotron structure meeting given specifications (energy, intensity, emittance of the beam, types of ion accelerated, high degree of stability, compactness, control of the spill, etc) may be based on various different types of solutions.

For compact, medium sized machines such as medical accelerators, the lattice may consist of two or four periods and the number of main dipoles and quadrupoles per period is a free parameter.

The injection in the ring does not impose severe restrictions concerning the optical structure, but careful attention must be given to the fractional value of the tune numbers in order to allow for the tune spread at injection due to space charge effects.

The extraction is more restrictive in the case of slow extraction on a third integer resonance, as specific elements such as extraction sextupoles, magnets or electrostatic septum deflector and other special systems must be inserted in the structure in locations which depend on the optical functions, which must also be very carefully adjusted.

It follows from this that the optimization of a high precision synchrotron for specialized applications requires considerable work which may require the involvement of several experts over a long period.

Such an task was undertaken at CERN from 1996 to 1999 before the start of the ETOILE project. The objective was to carry out the detailed design of an instrument optimized for light ion or proton therapy and to make it freely available to European countries ready to start the construction of a national facility.

As indicated in reference [7]:

"The Proton Ion Medical Machine Study (PIMMS) group was formed following an agreement between the Med-AUSTRON (Austria) and the TERA Foundation (Italy) to combine their efforts in the design of a cancer therapy synchrotron capable of accelerating either light ions or protons. CERN agreed to support and host this study in its PS Division. A close collaboration was also set up with GSI (Germany). The study group was later joined by Onkologie-2000 (Czech Republic). Effort was first focused on the theoretical understanding of slow extraction and the techniques required to produce a smooth beam spill for the conformal treatment of complex-shaped tumours with a sub-millimetre accuracy by active scanning with proton and carbon ion beams. Considerations for passive beam spreading were also included for protons".

Making use of this considerable body of work, and following the examples of the Italian (CNA), Austrian (Med-Austron) and Swedish (Karolinska Institute) projects, we have decided to adopt the PIMMS synchrotron for the French ETOILE project.

• Principle of the facility

The general structure of a hadrontherapy facility based on a synchrotron is given in figure II-1, and described in the following sections. Two sources produce ions which are pre-accelerated by a linear accelerator (linac) and are then injected in the synchrotron for acceleration to their nominal energy. The particles are then extracted and transported along beam lines to the treatment rooms, which are arranged in a "fishbone" structure. The active scanning system is located at the end of the line and can, if necessary, be replaced by a passive diffusion system.

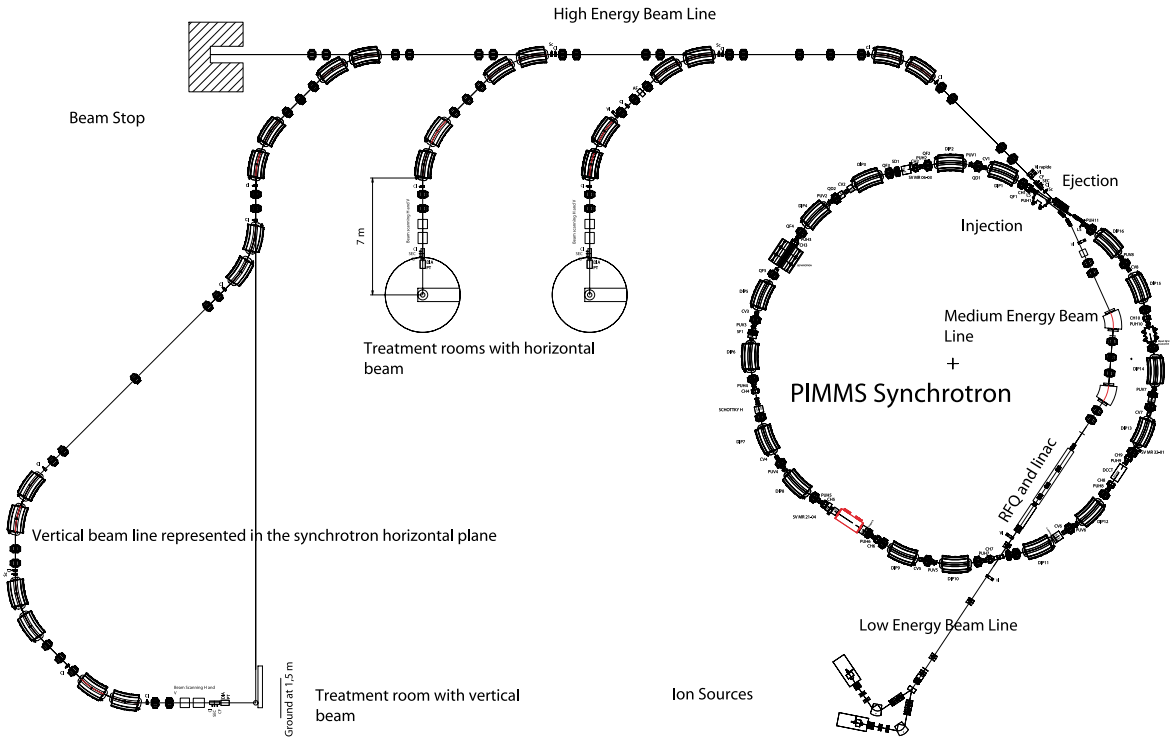


Figure II-1: general structure of the facility

• Machine cycle

The synchrotron operates in pulse mode in order to comply with the requirements for flexibility described earlier. The machine cycle can be varied from spill to spill and according to the characteristics of the volume to be treated. The values given below are approximate and we will refer to the tables of characteristics for specific values. The cycle can be broken down as follows:

Injection in the synchrotron: The beam from the source is chopped into a macropulse lasting less than 200 microseconds. These particles are injected in the ring in 33 microseconds by a standard multiturn injection process.

Acceleration : The particles are accelerated in the synchrotron up to nominal energy. This phase lasts a maximum of 0.7 s.

Plateau and spill: The cycle is maintained at an energy plateau until the end of the spill. It is triggered either at the start of the plateau (fixed tumour) or by a "gating" signal (mobile tumour) and can last from 0.2 s to 4 s depending on the requirement. The spill is obtained by a slow extraction system which makes it very homogeneous.

End of cycle: The hysteresis cycle of the magnetic elements is completed and is restored to the injection values. This final phase can last up to 0.5 s.

Each cycle is independent of the others. The machine is pulsed at a rate of less than one hertz.

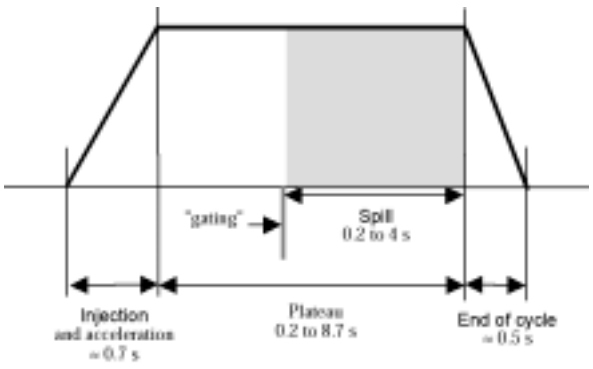


Figure II-2: simplified illustration of the machine cycle

• III •

Production of ions

The technology of the ion sources is established and can provide the ion species and intensities required, whether protons, helium, oxygen or carbon ions. The injection can use two "ECR" (Electron Cyclotron Resonance) type sources which fully meet the specifications for the ion species considered. These sources have permanent magnets and are the best choice in terms of cost and reliability since they require neither a power supply nor a high pressure cooling system.

• Carbon ions

Carbon ions are provided by an ECR source which can provide the charge states required (4 for carbon) before injection in the linear accelerator. This type of source was chosen by GSI for the Heidelberg hospital project.

This source is commercially available: for example SuperNanogan [8] whose main advantages are:

- Excellent long term stability of the current (± 1%) over at least 2 weeks with 200 µA of C^{4+}.
- Beam emittance of 180 p mm x mrad at 8 keV/amu (0.75 p mm x mrad normalized)
- Interchangeability. The injector is necessarily equipped with 2 sources, which can each be specialized for one type of ion or deliver the same ion. They are identical, which means that they can be maintained without interrupting the operation of the centre.

Figure III-1: 14.5 GHz SuperNanogan source with permanent magnets (dimensions ~ 0.5 x 0.5 x 0.5 m^3)

• Protons and molecular ions

Protons can generally be supplied by a discharge source or an ECR source. The intensities of molecular ions required are 1.2 mA with $^1H^{2+}$ and 800 µA with $^1H^{3+}$.The H^{2+}or H^{3+} are used to reduce the space charge (the extraction voltage is higher). They are converted to protons by stripping at the exit of the linac.

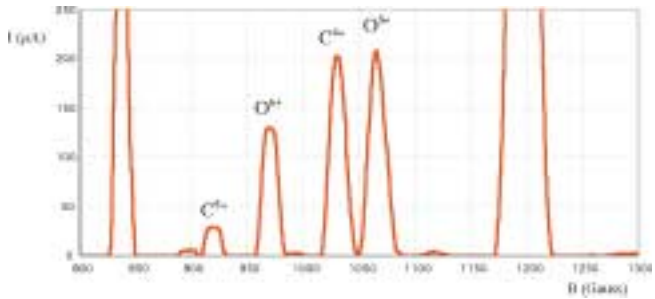


Figure III-2: typical spectrum (optimized for C^{4+}) of ions produced by SuperNanogan (I = 200 mA). Gas feed CO_2, extraction voltage 29 kV and RF power 114 W

• IV •

Injection system

IV-1
General introduction

The injection system shown in figure IV-1 runs from the production of ions in the sources to entry to the synchrotron via a low energy analysing line, a linear accelerator ("RFQ" + "linac"), a stripper and a medium energy line.

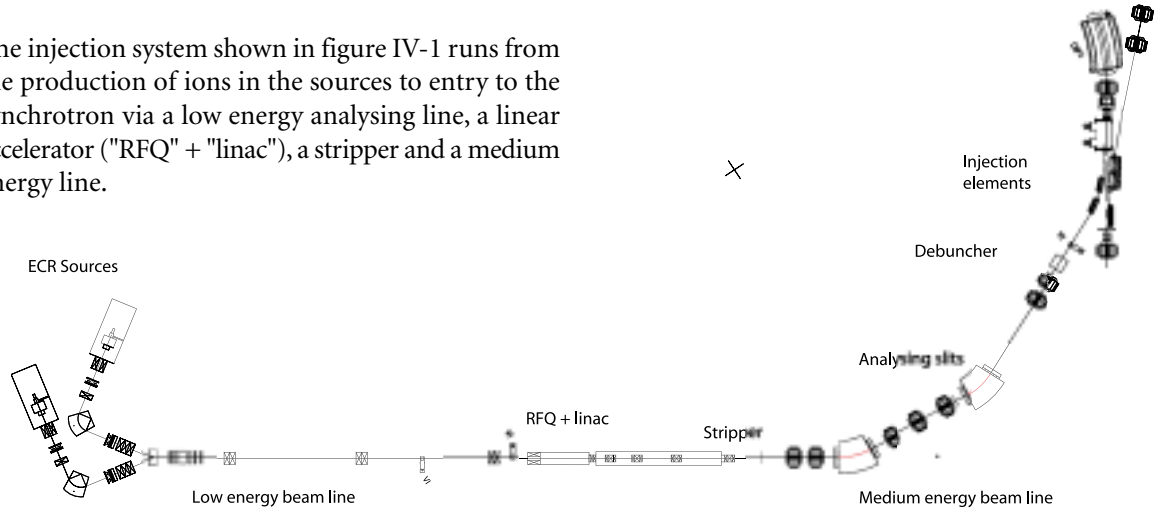


Figure IV-1: elements of the injection system

The injection system of the ETOILE project is based on that proposed for the facility dedicated to ion beam cancer treatment at Heidelberg (HICAT project) [9].

The injector of the HICAT project was designed several years ago, mainly by the GSI teams and the university of Frankfurt [9] [10] [11] [12] [13] [14]. This structure has been chosen as the reference for the preliminary design of the ETOILE project for a number of reasons. The architecture chosen is in fact as simple as possible (a single injector for protons and carbons) while providing a wide range of adjustments. It is therefore optimized with respect to costs (design, construction and operation). Even though some choices are very much connected with the actual experience of the laboratories involved in its design (RF frequency, "IH" structure), it is a very good solution for meeting the requirements of the ETOILE project specifications and to serve as a solid base for its costing.

The Heidelberg project version of this injector [10] is shown below in figure IV-2 [15]. We are using it in a similar configuration, but the PIMMS ring is different from the Heidelberg synchrotron. In our case, the RFQ + linac assembly is placed inside the ring in order to minimize the ground area used and the length of the medium energy beam lines. However, the ion sources are located outside, in a room the access of which is allowed during operation.

This injector accelerates carbon ions and protons, and also other types such as helium or oxygen.

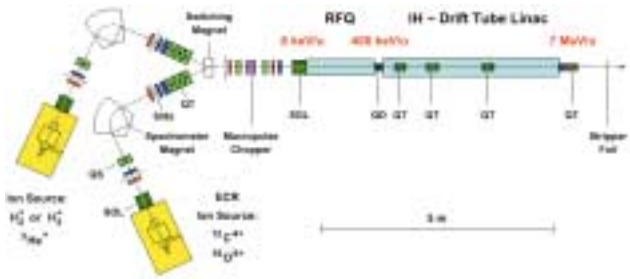


Figure IV-2: diagram of the HICAT project injector system (Heidelberg) [11] [15]. ECRIS = ECR ion source - SOL = Solenoid – QS = Quadrupole – QD = Doublet – QT = Triplet

In the ETOILE project, at the exit point of the ECR source, a transport and analysis device ensures the purity of the beam. The beam is transported, via the low energy line, to a compact accelerator assembly consisting of a radiofrequency quadrupole ("RFQ"), a matching section and a interdigitated ("IH") structure. It then passes through a thin carbon foil ("stripper") which gives it its final charge state (6+ for carbon ions). It is then carried to the injection point in the synchrotron via a medium energy beam line.

IV-2
Main parameters

Parameters	Carbon ions	Protons
Kinetic energy	7 MeV/uma	7 MeV
Duration of turn	2.06 μs	2.06 μs
Source current	125 μA $^{12}C^{4+}$	2.4 mA for protons 1.2 mA for $^{1}H_{2}^{+}$
Total standardized emittance	$< 1.2\ \pi\ 10^{-6}$ m x rad	$< 1.2\ \pi\ 10^{-6}$ m x rad
Dp/p at injection in the synchrotron	$< \pm\ 1.5\ 10^{-3}$	$< \pm\ 1.5\ 10^{-3}$
Current at injection in the synchrotron	105 μA with $^{12}C^{6+}$	1.38 mA
Injection time in the synchrotron	33 μs (16 turns)	33 μs (16 turns) [16]
Injection efficiency	23%	12%[16]
Repetition	< 1 Hz	< 1 Hz
Maximum duty cycle	4×10^{-5}	4×10^{-5}

Table IV-1: parameters of the injection system

IV-3
Description

- *Sources.* The use of two identical ECR sources gives the possibility to switch rapidly between ion species and also provides a backup source in the event of a fault.

- *Low energy line.* The beam from the source is analyzed by a magnetic spectrometer which is followed by a triplet of quadrupoles, making it possible to adjust the intensity of the beam in a range from 1 to 1000 by monitoring the losses on a diaphragm. There is then a switching magnet which selects the source, downstream of which is a chopper which adjusts the duration of the pulse injected in the RFQ.

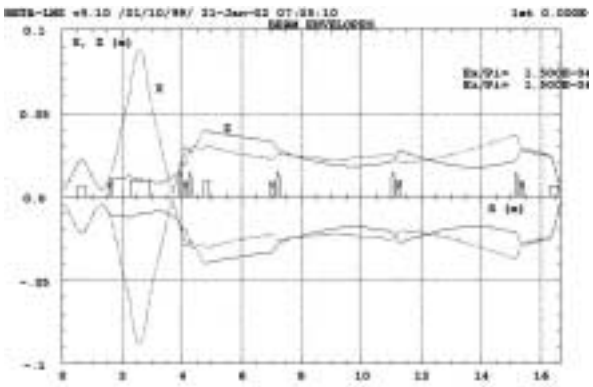


Figure IV-3: beam envelopes for the low energy line (excluding space charge)

The possibility of transport without losses, with space charge, of a H^{2+} beam (1 mA at 8 keV/amu) in the low energy line has been established by associating the quadrupoles in triplets and not in doublets. The beam has reduced oscillations and a diameter of around 70 mm [17].

- *RFQ.* A radio-frequency quadrupole ("RFQ") creates an initial acceleration from 8 keV/amu to 400 keV/amu. It is "4-rod RFQ" type, and was designed at the University of Frankfurt. It operates at 216 MHz with a peak RF power of 100 kW, and an electrode voltage of 70 kV [10].

- *A matching section* enables transition from the RFQ to the "IH-DTL" interdigitated structure which follows. It is also used to correct the beam trajectory and to measure some of its characteristics such as the intensity.

- *IH-DTL.* This second part provides acceleration from 400 keV/amu to 7 MeV/amu. It consists of a 3.8 m long cavity. The acceleration is provided by 56 accelerating gaps and focusing by 3 triplets. This part also operates at 216 MHz with a peak RF power of 1 MW, a maximum field on the axis of 18 MV/m and an effective acceleration voltage per gap of 450 kV maximum [10].

We refer to [10] for further details concerning the characteristics of this injector.

- The medium energy line transports ions at 7 MeV/amu from the exit point of the linac to injection in the ring. It has, amongst other elements, a triplet focusing the ions on the stripper (consisting of a 50 µg/cm^2 thick carbon foil), an association of a doublet with a deflecting magnet, a triplet, another association of a deflecting magnet with a doublet [18]. This assembly transport the ions to the entry point of the injection elements in the synchrotron.

These elements consist of two septum magnets preceding the final electrostatic injection septum. The total deflection is 90 degrees. The medium energy line then finally is fitted with a debuncher which reduces the $\Delta p/p$ of the ions injected to $\pm$ 1.5 x 10^{-3} (it was $\pm$ 2 x 10^{-3} at the exit of the stripper) and analysing slits. The debuncher cavity of the HICAT project has been chosen [19] : a quarter-wave coaxial resonator with two accelerator gaps, 270 mm long.

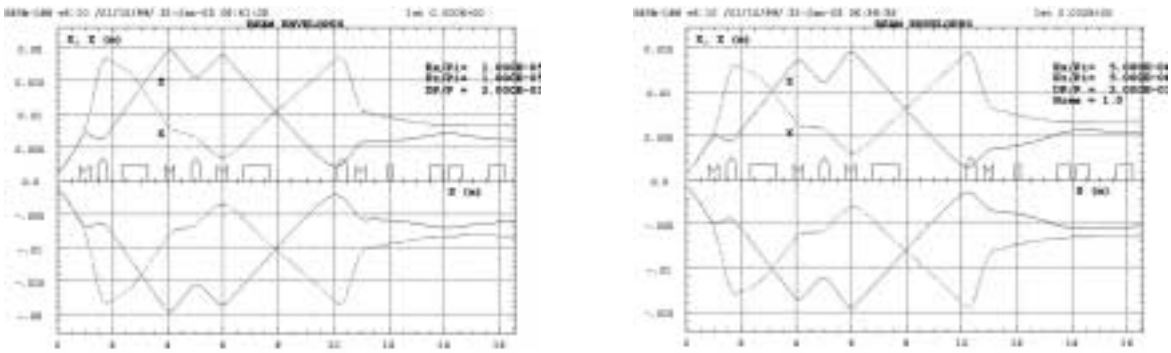


Figure IV-4: beam envelopes (carbon ions and protons) for the medium energy line

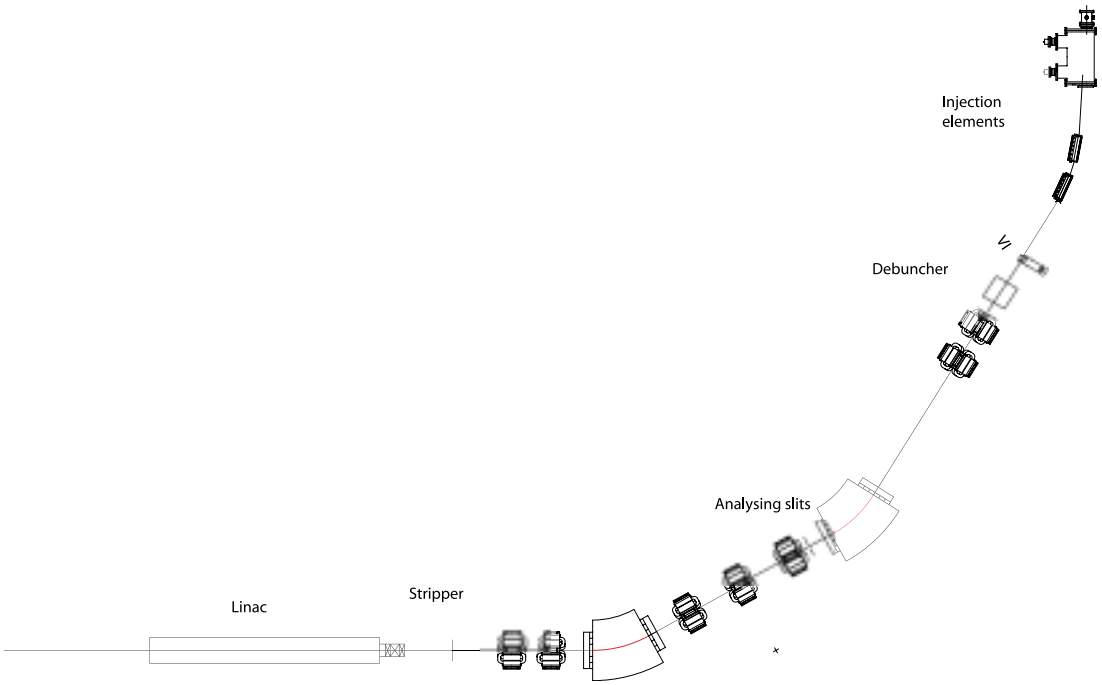


Figure IV-5: diagram of the medium energy line

• V •

Synchrotron

As already stated, the PIMMS synchrotron is the main element of the ETOILE hadrontherapy facility.

Given the considerable amount of work and the numerous publications by the PIMMS team, we will not attempt to give a detailed review of all the technical considerations which led to this machine optimized according to current state of the art. However, certain basic choices determining the philosophy for the design and operation of the accelerator are given here:

- multiturn injection (proposed by CNA) for filling the ring with carbon ion (or proton) beams which, after acceleration, have constant transverse emittances over almost the whole range of extraction energies,

- use of a betatron core, a concept invented and developed for the SATURNE 2 synchrotron at Saclay [20], to bring the beam to the resonance while keeping the optical parameters of the machine unchanged during the extraction process.

V-1
Main parameters

The ring has a circumference of 75.24 m and has an optical configuration with separate functions composed of FODOF type cells. The magnetic structure consists of 16 H-type dipoles with a maximum field of 1.5 T and 24 quadrupoles with a moderated maximum gradient of 3.65 T/m.

The optical structure has a superperiodicity of two in order to give two dispersion free long straight sections in which the accelerator cavity, the resonant sextupole and the injection and extraction septum elements are located. This makes the ring as compact as possible.

The quadrupoles are divided into three families to enable the tune numbers to be adjusted to the values required for injection or extraction while maintaining the dispersion function at zero in the two long straight sections. Apart from the resonant sextupole, four other sextupoles are placed in the dispersive parts of the ring to control the chromaticity. This is important to prevent instability of the beam due to the space charge at injection and to adjust the Hardt condition which determines the extraction quality.

The main parameters of the synchrotron are summarized in Table V-1 and the diagram showing the main components is given in figure V-1.

Compared to the wide range of other machines of an equivalent size, the PIMMS synchrotron presents relatively smooth focusing optics which results in low sensitivity to field errors. This is particularly important for medical machines, in particular if the active scanning technique is used as the uniformity of the spill by slow extraction may be significantly affected by dynamic field errors.

The synchrotron cycle (that is the cycle of the magnetic field of the magnets and the acceleration) contains the following basic phases, as described earlier: field increase from the resting level to injection energy, injection plateau, acceleration to extraction energy, extraction level, field increase to peak value of the hysteresis cycle of the magnets, return to resting level. This procedure ensures good reproducibility of the magnetic field from cycle to cycle. The typical durations of the various phases are given in Table V-2. The total of all these phases gives a cycle of 1.5 to 10 seconds for a spill of 0.2 to 4 seconds.

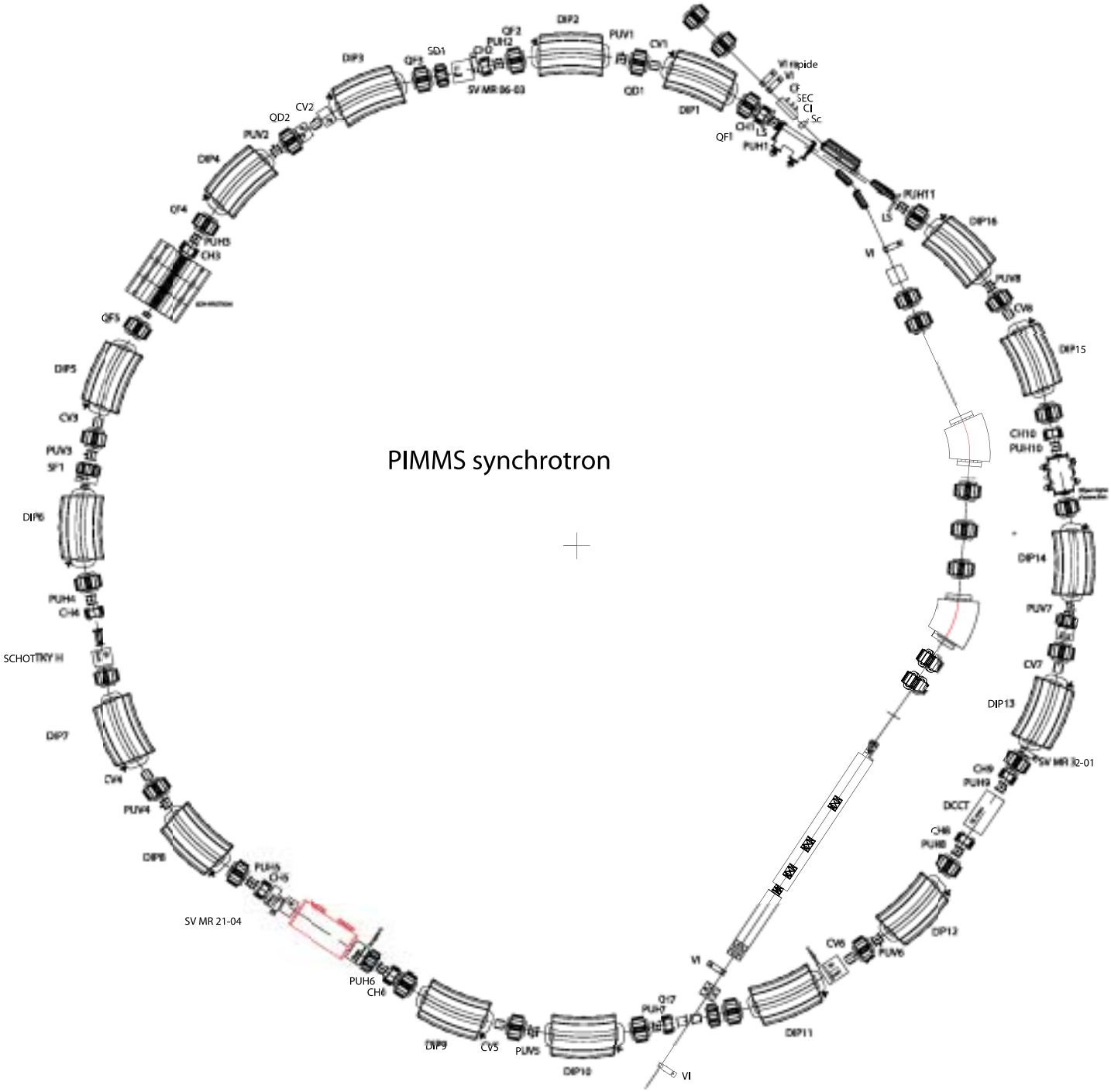


Figure V - 1: the PIMMS synchrotron

Maximum energy (carbon)	400 MeV/uma
Injection energy (carbon and protons)	7 MeV/uma
Circumference	75.24 m
Superperiodicity	2
Number of dipoles	16
Maximum field	1.5 T
Bending radius	4.23 m
Number of quadrupoles	24
Maximum gradient	3.65 T/m
Length	0.35 m
Number of sextupoles	5
Chromaticity/resonant, maximum strength	54/85 T/m^2
Length	0.2 m
Horizontal/vertical tune numbers	νx/νz
Injection, carbon	1.68/1.72
Injection, proton	1.764/1.829
Extraction	1.6666/1.72
Maximum horizontal/vertical optical functions	βx/βz
Injection, proton	17.1/17.2 m
Nominal	16.1/14.8 m

Table V-1: machine parameters

Increase to injection	70 ms
Injection plateau	50 ms
Acceleration to maximum energy	700 ms
Magnetic field plateau	200 à 8680 ms
Including slow extraction of the beam	200 à 4000 ms (min. to max.)
End of hysteresis cycle	500 ms maximum
Total	1.52 s à 10 s

Table V-2: synchrotron cycle

V-2
Injection

As already seen, the HICAT injector has been proposed for the ETOILE project. This choice, already also made by the CNA project [21] [22], has clear advantages in terms of development, equipment and construction costs, but raises new problems concerning the injection of the proton beam necessary for irradiation by passive diffusion.

Two limitations must be taken into account:

- Acceptance of the ring imposed by the aperture of magnetic elements already defined in PIMMS,
- The tune spread due to the proton space charge, which must not exceed the value reached at 20 MeV for 2 x 10^{10} particles at the patient and per spill (also the case with PIMMS).

The first limitation is easily overcome as the emittance of the proton beam stored at 7 MeV, which must be 21 π 10^{-6} m x rad (cf. Table V-3) remains less than that of the carbon beam at injection, i.e. 30 π 10^{-6} m x rad (figure V-2). In fact, for protons, the emittance at 7 MeV is inferred from the emittance at 20 MeV (12.5 π 10^{-6} m x rad) by a factor equal to the ratio of the Lorentz coefficients βγ (20 MeV)/βγ (7 MeV) = 1.7. This ensures that the proton and carbon emittances are equal over the whole of the range of extraction energies of PIMMS.

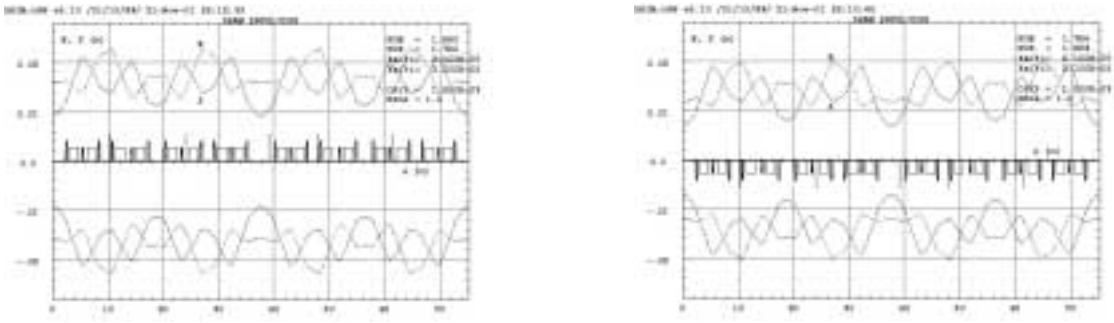


Figure V-2: horizontal and vertical envelopes of the beam stored at injection. Top: carbon, $\varepsilon x = \varepsilon z = 30\ \pi\ 10^{-6}$ m x rad.
Bottom, protons, $\varepsilon x = \varepsilon z = 21\ \pi\ 10^{-6}$ m x rad. The emittances are total emittances. The beam transport and focusing elements are represented schematically near the axis.

	Energy (MeV/uma)	βγ (Lorentz)	$\beta\gamma/\beta\gamma\vert_{7MeV/uma}$	Bρ (T x m)	$\varepsilon_{x,z}/\pi$ (10^{-6} m x rad)
Carbon	7	0.123	1	0.763	30
	85	0.437	3.56	2.714	8.44
	120	0.524	4.26	3.254	7.04
	400	1.022	8.32	6.346	3.61
Protons	7	0.122	1	0.383	21.2
	20	0.208	1.70	0.650	12.5
	50	0.331	2.70	1.040	7.84
	60	0.363	2.97	1.137	7.14
	220	0.724	5.91	2.265	3.58

Table V-3: energies, momenta, rigidities

The second limitation disappears because the number of protons in each spill (10^{10} at the patient) is reduced by a factor of two[2] in relation to the nominal value of PIMMS. This reduction of intensity combined with the increase in emittance leads to a tune shift which is almost unchanged despite its significant dependence on energy. The consequence of this is that the operating point in the tune number diagram does not have to be changed. In fact, the tune number slip Dn is proportional to $N/S\beta^2\gamma^3$ where S is the cross-section of the beam and N is the number of particles stored. Thus, the cross-section of the beam varies as $1/\beta\gamma$, and therefore increases by a factor of 1.7 between 20 and 7 MeV. Reducing N by a factor of 2 gives tune numbers $\nu_x = 1.751$ and $\nu_z = 1.813$, which are very similar to those expected at 20 MeV $\nu_x = 1.764$ and $\nu_z = 1.829$ ([7], page 70).

Figure V-3 illustrates the dispersion of tune numbers .

[2] This only moderately increases the irradiation time in passive mode, which is in principle much faster than active mode.

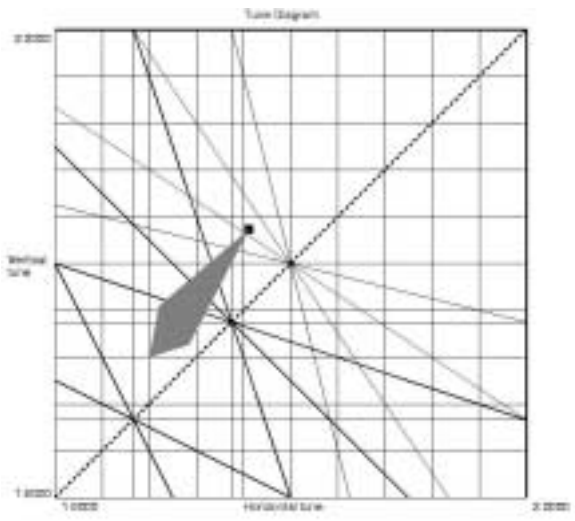


Figure V-3: dispersion of tune numbers due to the space charge for 7 MeV protons

In view of these results, a new multi-turn injection layout with 7 MeV protons has been optimized [16] [23], in relation to the initial PIMMS scenario, without having to make any major changes to the injection parameters, summarized in table V-4.

	Carbon (active)	Protons (active et passive)
Injection energy	7 MeV/uma	7 MeV
Particles stored	8×10^{8}	3.4×10^{10}
Injection	16 turns	16 turns
Injection efficiency	23%	12%
Emittance stored	$30\ \pi\ 10^{-6}$ m x rad	$21\ \pi\ 10^{-6}$ m x rad

Table V-4: injection parameters

Note:

At 7 MeV the sensitivity of the closed orbit to field errors is clearly greater than at 20 MeV. However the example of the MIMAS machine (injector for the SATURNE 2 machine) demonstrates the feasibility of injection of 390 keV protons without any particular difficulty. As a comparison with PIMMS, the field in the MIMAS dipoles was 8.0×10^{-2} T, and the gradient in the quadrupoles was 4.1×10^{-2} T/m [24]. The injection was carried out over 130 turns, and took around 1 ms (compared with 16 turns and 33 μs for ETOILE). The closed orbit at injection was corrected without any problem from ± 10 mm before correction to ± 1 mm with correction.

V-3
Extraction

Slow extraction is a conventional way of extracting the stored beam from the synchrotron. It consists of inducing an unstable movement of the particles for a rational value of the horizontal tune number. Half-integer resonance and third-integer resonance can both be used. For medical machines third-integer resonance is preferable as it produces a slow spill which is easier to control. This is important for irradiation of deep-seated tumours using active scanning and for on-line dosimetry.

Slow extraction requires special equipment. In the case of the PIMMS synchrotron, a sextupole induces an instability in the horizontal movement when the tune number is close to 5/3, a betatron core slowly drives the beam onto the resonance and an electrostatic septum deflects the large amplitude particles in the direction of the extraction channel. This process provides a high level of homogeneity in the spill.

Some restrictions are imposed on the optical functions at the location of the instability excitation sextupole and the electrostatic septum in order to satisfy the "Hardt" condition which improves the extraction efficiency and the quality of the beam extracted.

This concept of forced-acceleration extraction based on the use of a betatron core was developed and perfected 20 years ago for the SATURNE 2 synchrotron at Saclay [20]. The extraction process is easier to control with this technique as all the optical elements of the machine are kept constant, with the only dynamic system being the power converter of the betatron.

Another possibility for performing slow extraction is to excite the movement of the particles using a transverse radio-frequency field. This technique, known as "RF knock-out", has been successfully tested at GSI [25]. It is proposed for the HICAT project, and is currently routinely used at the CHIBA/HIMAC medical accelerator. It could also be considered for ETOILE.

A comparison of these two techniques should be carried out within the context of a detailed preliminary design, examining the following points.

- Regularity and uniformity of the spill which could be affected by fluctuations in power supply. These problems can however be controlled by real-time dosimetry at patient level.

- Possibility of modulating the intensity and even momentarily interrupting the spill within one cycle in the case of non-connected tumour sections.

• VI •

High energy beam lines

VI-1
Introduction

A "fishbone" structure has been chosen which is advantageous in terms of modularity, adjustment and possibility of extension [26]. It makes the installation of additional rooms easier if required. A general view is given in figure VI-1.

The 150 metres of lines are made up of independent achromatic basic modules giving regular and repetitive beam envelopes. There are three basic modules which enable easy adjustment of the beam diameter in each of the treatment rooms. This is an advantage for a medical machine which must be totally automated.

The beam quality can be tested at the downstream end of the fishbone. This solution is also recommended for the Heidelberg centre. It is considered an advantage by certain French medical physicists for the same reasons [27].

The scanning system has been positioned downstream of the last deflection dipole on each line. An upstream scanning system would require a final dipole with a larger pole and air gap. The solution proposed makes maintenance easier and enables the use of identical dipoles in the high energy lines. The advantage is practical as well as economical. On the other hand it does lead to additional building costs, as the line with vertical beam is higher.

To carry out the calculations, the origin of the high energy lines has been taken, as in PIMMS, at the entry of the electrostatic injection septum, around 11 metres upstream from the actual separation of the vacuum chambers of the ring and of the high energy lines. This makes it possible to define the original optical conditions based directly on the characteristics of the slow extraction process.

VI-2
Principles

The design principles of the high energy lines can be summarized as follows:

- The PIMMS structure is retained up to the first quadrupole "QFA" of the extraction section.
- A 3.8 m long straight section is left free from all equipment downstream of the "QDB" so that a handling vehicle can pass, by simple removal of the vacuum chamber.
- An initial section deflects the beam by 45 degrees to inject it into the fishbone itself. It contains a fast beam stopping system, described below.
- The basic modules are achromatic, and are characterized by identical beam properties at both ends: same diameter (varying from 4 to 10 mm) and low divergence.
- The deflections are performed by 22.5 degree, 1.66 m long C-dipoles which are all identical and have parallel faces.
- All the quadrupoles are identical, 0.35 m long with a 20 T/m maximum gradient.
- The size of the beam at the origin of the high energy lines is:
  - in the horizontal plane:
  10 mm total, regardless of the energy and the type of particles
  - in the vertical plane:
  17.4 to 11.4 mm for carbon,
  from 85 to 400 MeV/amu
  16.8 to 11.3 mm for protons, from 50 to 220 MeV
- The total momentum dispersion is 1.1×10^{-3}
- The size of the beam at the patient is adjustable from 4 to 10 mm.

VI-3
Description of the optics

Extraction section (figure VI-2)

This section, which is 29.50 metres long, transport the beam from the electrostatic extraction septum to the fishbone. Its geometry is that of PIMMS up to the first quadrupole QFA, which is followed by a matching quadrupole QDB, then a 3.8 m long free section to allow a handling vehicle to pass through. This is followed by a pair of quadrupoles QDC/QFD, then a 45 degree deflection which guides the beam via the last three quadrupoles, QF1/2/3, to the fishbone exit. The dispersion function is identically set to zero downstream from the deflection using quadrupoles QFA/QDB/QDC and QFD only. The beam is matched to the fishbone exit characteristics at the exit point of QF3 by the seven quadrupoles QFA to QF3.

90 degree deflection module

This module, which is 21.19 metres long, provides horizontal deflection towards the treatment rooms (figure VI-2), and vertical deflection at the downstream end for the vertical line (figure VI-4).

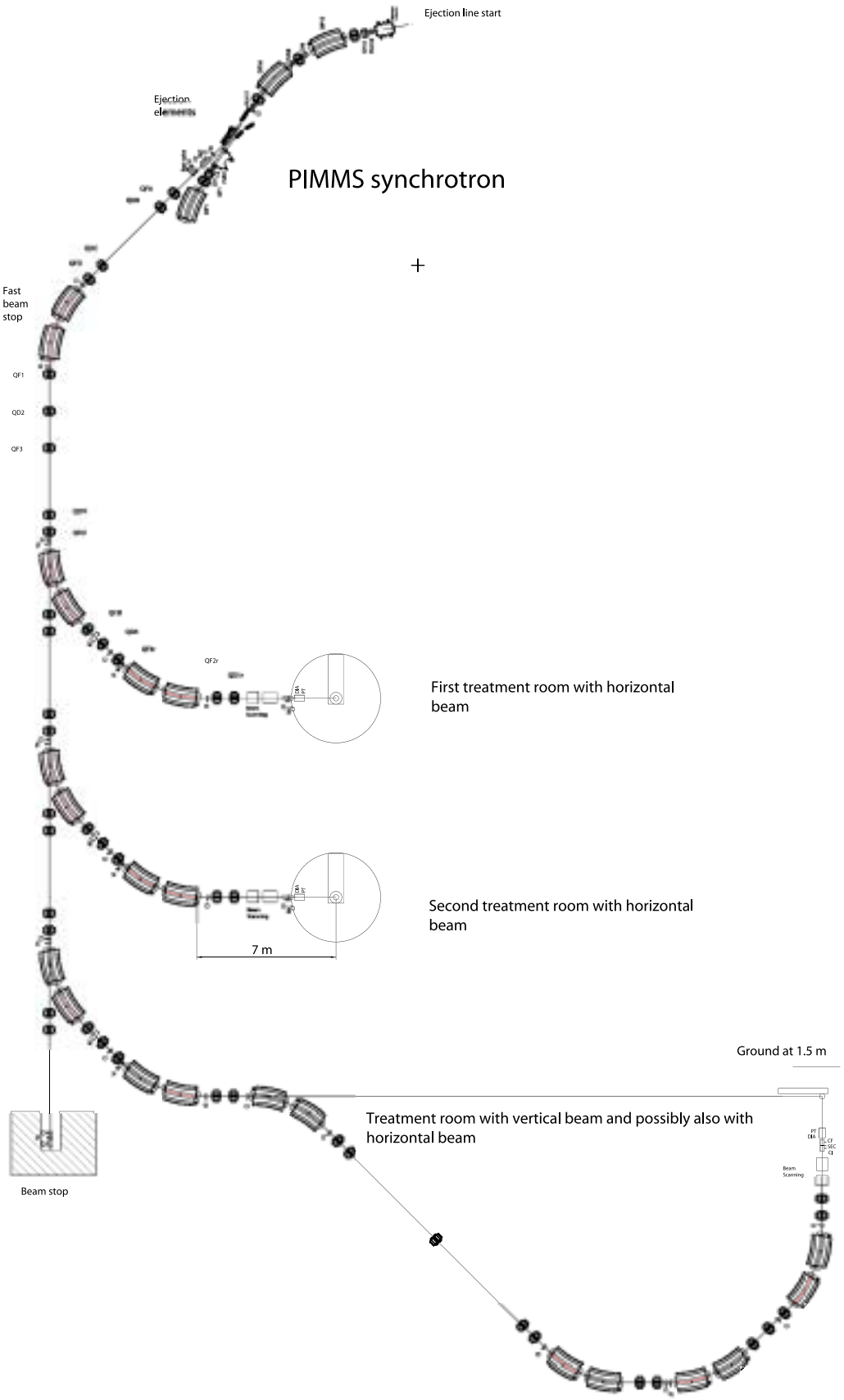


Figure VI-1: high energy lines and beam distribution in the treatment rooms (the vertical line is drawn in the horizontal plane)

The module is symmetrical both geometrically, as shown in the figure, and optically. The quadrupoles, and thus their power supplies, are connected in pairs QP1l-QP1r, QP2l-QP2r, QP3l-QP3r.

The two pairs of quadrupoles at the beam line extremities are only used for adjusting the beam diameter, while the central triplet also ensures the achromatism of the module. It should be noted that the downstream straight section (i.e. on the patient side when using the module at the end of the line) can be extended by 50 cm or more if necessary, while maintaining the coupling of the quadrupoles, with no major deterioration of the beam characteristics at the patient.

FODO module (figure VI-4)

The "FODO" module, which is 10 metre long, is used to transport the beam between the deflection modules and along the various straight sections. It consists of four quadrupoles connected in two pairs, QDl-QDr and QFl-QFr.

It is used for the periodic transport of the beam envelope using a transfer lattice -I (where I is the identity matrix). This FODO geometry can also be used in the room with the vertical beam if a decision is made later to add a line with horizontal beam.

“S” vertical module

This module, which is 22 metre long, starts and ends with a pair of 22.5 degree dipoles, which take the beam from the lower horizontal plane to the upper vertical deflection. The beam is matched by a set of five quadrupoles. A module of this type will not be used in the design of a rotating isocentric gantry.

Fast stopping device

Figure VI-5 describes this system ("beam chopper") which is included in the 45 degree deflection of the extraction module. In normal operation the beam follows a trajectory along a chicane made of 4 fast dipoles BM1 to BM4 (magnetic length 0.3 m, deflection 6.6 mrad, see location in figure VI-2).

In the event of a stop, the fast dipoles are cut in less than 200 microseconds and the beam is sent to a beam dump located in the centre of the chicane. This design allows to prevent any beam shift at the patient during the stopping.

VI-4
Description of the high energy beam lines

From extraction to the first room

This line, which is 50.7 m long, consists of the extraction section and a horizontal deflection module. The structure is given in figure VI-2, together with the beam envelopes for a 10 mm diameter (the structure enables a range of 4 – 10 mm) at the patient.

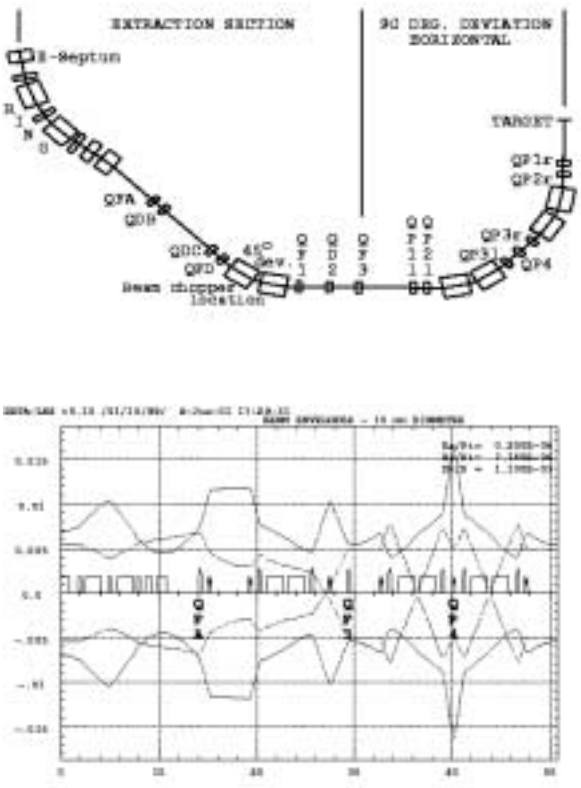


Figure VI-2: beam delivery to the first room (horizontal beam)

From extraction to the second room

This line, which is 58.7 m long, consists of the extraction section, followed by a FODO module, then a 90 degree horizontal deflection module. The structure is given in figure VI-3, together with the beam envelopes for a 10 mm diameter at the patient.

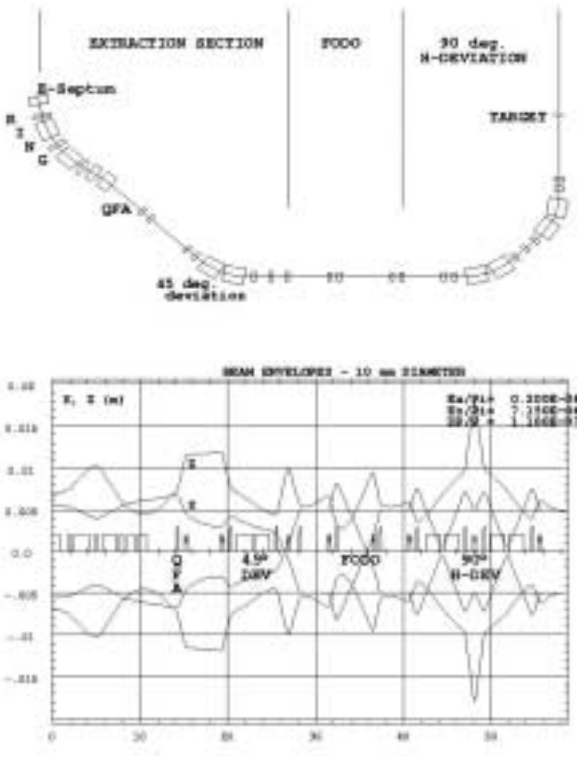
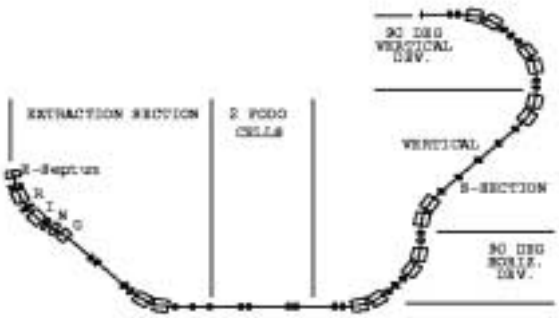


Figure VI-3: beam delivery to the second room (horizontal beam)

From extraction to the room with vertical beam

This line, which is 98.70 m long, consists of the extraction section, two FODO modules, a horizontal deflection module, an "S" module which transport the beam from the horizontal plane at the machine to the final vertical deflection module which directs the beam to the target volume. Figure VI-4 gives the beam envelopes for a 10 mm diameter on the target.

The structure of the line with vertical beam is such that a horizontal line can be added at a later stage in the same room, connected at the exit point of the " S" section.



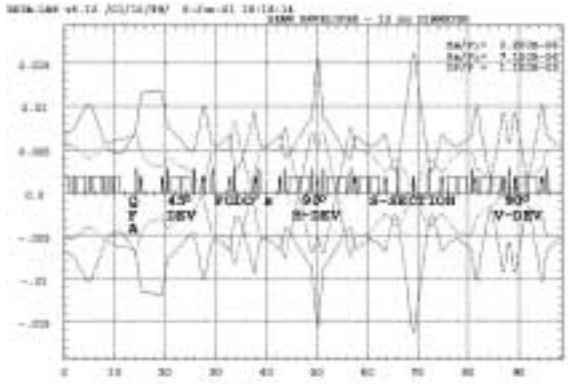


Figure VI-4: beam delivery to the room with vertical beam

Fast beam stop

The horizontal beam envelope is given in figure VI-5, as an example with optical adjustment to the maximum dimensions.

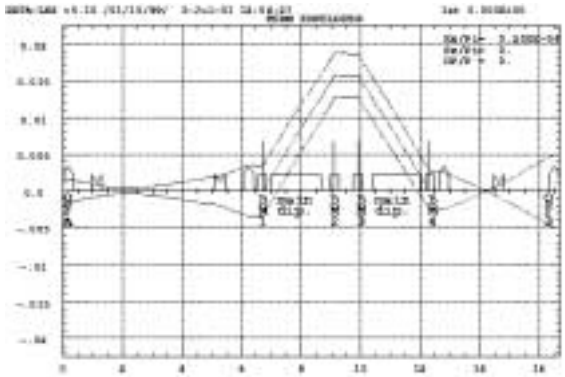


Figure VI-5 : central trajectory and beam envelope in the chicane providing the fast stop (for a maximum horizontal dimension)

VI-5
Option with rotating isocentric gantry

Until now the scenario which has been described has been based on fixed beam lines, as required in the specification. However, a vertical fixed line in any case requires fairly large transport optics and a fairly large building. The estimation of the overall financial cost of a scenario with rotating isocentric gantry is therefore justified, while remaining within the framework of a simplified preliminary design.

This additional study has been carried out in less detail than for the fixed lines, based on:

- the proposed structure for the HICAT gantry [28],
- budget estimates made for lines with fixed beam (optical elements, power supplies, command and control, building),
- an estimate of the terminal dipole.

The main unknown factor is the price of the rotating

structure. A preliminary mechanical study has been carried out in order to estimate the weights involved. This study needs to be carried out in more detail. The following conclusions have been drawn:

- transport line: 120 tons
- counterweight: 80 tons
- support structure: 400 tons

giving a total estimated weight of 600 tons.

The price of the support structure has been estimated taking the following basic costs into account:

- design
- construction (industrial documentation, process quality test runs, manufacturing, heat treatment, test assembly and transport)

The plan of the building corresponding to the replacement of the line with vertical beam by a line with rotating gantry is given in XVI-6. The only modifications in terms of civil engineering are for the gantry part. The additional cost for this option is approximately 8.2 M¤ (including the building).

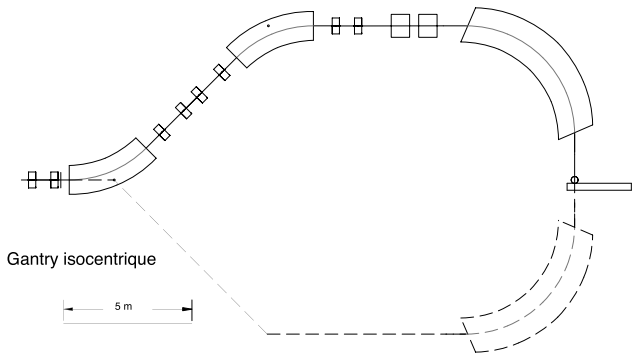


Figure VI-6: outline diagram of the gantry (from GSI)

The scanning system is installed upstream of the terminal dipole in order to minimize the total diameter of the rotation system.

The optics of this assembly will be incorporated in the modular design of the fixed lines (achromatism, adjustable beam diameter) which must be able to compensate for the consequences of rotation of the arm on the beam characteristics at the isocentre.

• VII •

Technical devices and components

VII-1
Transport and focusing elements of the synchrotron

The various elements are those described in the PIMMS document ([7] part 2). They are the result of a detailed study which will not be covered again here. They have however been the subject of a budget estimate either from manufacturers for standard elements or for the betatron core, or consultation with specialists from CERN [29] for special elements such as septum deflectors. Septum deflectors require a high degree of technical skill, as does the betatron core.

VII-2
Transport and focusing elements for the high energy lines

A comprehensive study of the beam envelopes has been carried out for all operating conditions (energy and diameter) and has led to definition of the optical elements and the vacuum and diagnostics systems. It has thus been possible to define the useful aperture which corresponds to the maximum transverse size of the beam with the addition of a safety margin.

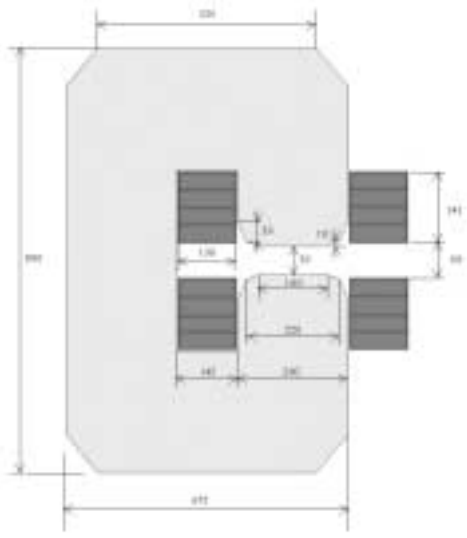


Figure VII-1: standard cross-section of a dipole

The quadrupoles required are the same as those proposed for the PIMMS extraction line ([7] volume 2 appendix II V). The magnetic length is 0.35 m for a maximum field gradient of 20 T/m.

The dipoles are new, with C-type dipoles being used, and are all identical. The main characteristics are given below [30]. The technology used and the magnet assembly remain those which were defined for the PIMMS beam line magnet. It will consist of a stack of identical laminations whose profile is determined by the standard cross-section. All the laminations will be assembled on a circular template corresponding to the bending radius of the magnet.

The characteristics of the dipole are given below. It has been designed in 2-D using OPERA-2D code.

Type	C	
Number	22	
Overall length	1.8930	m
Iron length	1.661	m
Overall width	0.815	m
Overall height	0.880	m
Air gap	0.0560	m
Weight	7.25	t
Nominal field	1.5	T
Maximum field	1.57	T
Maximum current	610	A
Magnetic length	1.661	m
Radius	4.231	m
$\Delta B/B$ tolerance	$\leq \pm 5 \times 10^{-4}$	
Horizontal "good field" region	±31	mm
Vertical "good field" region	±28	mm
Resistance (coils in series)	0.0488	Ω
Inductance (coils in series)	0.159	H
Number of coils	2 (1/pole)	
Number of turns	128 (64/coil)	
Number of water circuits in //	8 (4/coil)	
Average length of one turn	4.157	m
Length of one water circuit	67.6	m
Total power	18.2	kW
Temperature rise ΔT	12.7	°C
Flow rate	20.5 (2,56/circuit)	l/min
Pressure drop ΔP	6.44	bar

Table VII-1: characteristics of a dipole for high energy lines

VII-3
Power supplies

All the power supplies of the synchrotron are based on the characteristics of the PIMMS optical elements. The project only uses standard tolerances (5×10^{-5}) for the following reasons :

- The technologies used must be controlled, reliable and optimized from an economic point view,
- The spills obtained by the proposed extraction method have been measured on the SATURNE 2 machine and have demonstrated a high degree of consistency,

- Any micro-breaks in the spill can be compensated by real-time control of the delivered dose in order to ensure its consistency.

The quadrupoles of the high energy lines are fed separately. Their power supplies are defined by the characteristics given in the PIMMS project.
The dipoles of the high energy beam lines are supplied in pairs [31]. The characteristics of their power supplies are given in table VII-2.

Characteristics	60 V / 610 A
Regulation	5 x 10^{-5}
Mains supply	3 x 400V
Cooling	Eau
Dimensions (width, depth, height)	60. 80, 160 cm
Weight	500 kg
Number	11 (pour 22 dipoles)

Table VII-2: characteristics of the dipole power supplies in the high energy beam lines

VII-4 Vacuum systems

The vacuum systems associated with the synchrotron and beam lines are described below.

The conclusions can be used to define a coherent pumping system which corresponds to the criteria of an "industrial" type machine with maximum reliability and optimum efficiency.

VII-4-1 Synchrotron

Required pressures

An average pressure of 5 x 10^{-7} Pa will enable carbon ions and protons to be transported in the synchrotron with minimum losses (due to collisions with the molecules of residual gas).

Guidelines which led to the proposed structure

In order to minimize the time for which the machine is not available in the event of an accidental rise in pressure, the following principles have been adopted:

- the desorption rate used to calculate pumping is 1 x 10^{-7} Pa.m.s^{-1}. This is the rate for a clean chamber which is not baked,
- the construction of the vacuum chambers will use technologies which allow baking at 120°C for a few hours. In this way it will be possible to restore the nominal pressure quickly and safely if the synchrotron returns fully or partially to atmospheric pressure,
- all the pumping is carried out using ion pumps which require no maintenance.

Vacuum chambers

The calculations are made using the dimensions of the vacuum chambers of the PIMMS project. These chambers are made of stainless steel. The connections between the elements are Conflat® type flanges with copper seals. The vacuum chambers of the dipoles are corrugated.

Vacuum and measurement devices

Table VII-3 summarizes the main characteristics of the pumping system. The synchrotron is divided into 3 sectors by isolation valves. Each sector has a roughing vacuum system with the associated pressure measurements. High vacuum techniques should be used for cleaning and assembly. Venting to atmospheric pressure will be achieved using dry nitrogen.

Pressure measurements are taken using Pirani, Penning and Bayard Alpert pressure gauges. A gas analyzer will be used to qualify and quantify partial pressures. The safety functions are controlled by Pirani and Penning pressure gauges.

Baking system

This consists of single heating elements whose power is adapted to each vacuum chamber. The corrugations of the chambers of the dipoles reduce the thickness of the wall (the impedance thus becomes non-negligible) which can then be used as a heating element. In all cases, no costly regulation system is required, simply a few monitoring thermocouples.

Pre-evacuation	3 dry mechanical pumps (15 m/h) 3 turbomolecular pumps (150 l/s) 3 Pirani pressure gauges + power supply 3 Penning pressure gauges + power supply 3 x CF 100 isolating valves for the TMP
Pumping	15 ion pumps 400l/s 3 x CF 160 isolating valves for the sectors
Measurements	3 Pirani pressure gauges + power supply 3 Penning pressure gauges + power supply 9 Bayard Alpert pressure gauges + power supply 1 gas analyzer
Baking	Heating elements

Table VII-3: vacuum systems of the synchrotron

VII-4-2 Beam lines

From the point of view of vacuum quality, different separate sections are planned. Each line has its own roughing and pumping system. Diaphragms are placed close to the intersections with the synchrotron in order to minimize the flux of gas from the lines due to the differences in pressure. Pressure measurements are taken using Pirani, Penning and Bayard Alpert pressure gauges. Safety functions are provided using Pirani and Penning pressure gauges.

As for the synchrotron, the desorption rate used for the calculations is 1×10^{-7} Pa.m.$^{s-1}$. However, no baking system is planned.

Likewise, high vacuum techniques must be carefully applied (cleaning, assembly, dry nitrogen for venting to atmospheric pressure).

VII.4.2.1 Pomping system for low energy line

The low energy line contains the two ion sources and all the vacuum chambers up to the isolation valve before the intersection with the synchrotron.

Required pressures

The distribution of the pumping system in the low energy line makes it possible to adapt the pressure at the source side (1×10^{-3} Pa) to the pressure which must be maintained in the synchrotron on the isolating valve side (5×10^{-7} Pa).

Vacuum and measurement devices

In the sources, pre-evacuation and pumping are carried out by mechanical and turbomolecular pumps. In the rest of the line, the pre-evacuation system consists of a mechanical pump and a turbomolecular pump with the associated measurement equipment. Pumping is carried out using cryogenic pumps which absorb the high flux coming from the sources.

A diaphragm, the size of which is determined according to the profile of the beam, is placed immediately upstream of the isolating valve to reduce the flux entering the synchrotron.

Table VII-4 summarizes the main characteristics of the pumping elements.

Source pre-evacuation and pumping	6 mechanical pumps (15 m³/h) 6 turbomolecular pumps (450 l/s) 6 Pirani pressure gauges + power supply 6 Penning pressure gauges + power supply 6 x DN 150 isolating valves for the TMP
Line pre-evacuation	1 dry mechanical pump (15 m³/h) 1 turbomolecular pump (150 l/s) 1 Pirani pressure gauge + power supply 1 Penning pressure gauge + power supply 1 x CF 100 isolating valve for the TMP
Line pumping	3 cryogenic pumps 1500 l/s 1 x CF 100 isolating valve for the sections 3 Pirani pressure gauges + power supply 3 Penning pressure gauges + power supply 3 x DN 200 isolating valves for the cryo. pumps 4 x DN 100 isolating valves for the sections
Line measurement	1 Pirani pressure gauge + power supply 1 Penning pressure gauge + power supply 1 Bayard Alpert pressure gauge + power supply

Table VII-4: vacuum systems for the sources and the low energy line

VII.4.2.2 Vaccum systems for the linac and the medium energy line

These assemblies are isolated by valves on either side of the synchrotron.

Required pressure

The average pressure required in the medium energy line is 1×10^{-6} Pa.

Vacuum chambers

As with the synchrotron, the vacuum chambers are made of stainless steel. The junctions have metal seals. High vacuum techniques must also be applied.

Vacuum and measurement devices

A pre-evacuation system will be provided, with the associated measurement equipment and a secondary pumping system with ion pumps.

Table VII-5 summarizes the main characteristics of the pumping elements.

Pre-evacuation	1 dry mechanical pump (15 m^3/h) 1 turbomolecular pump (150 l/s) 1 Pirani pressure gauge + power supply 1 Penning pressure gauge + power supply 1 x CF 100 isolating valve for the TMP
Line pumping	4 ion pumps 400 l/s 2 x CF 160 isolating valves for the sections
Linac pumping	4 ion pumps 150 l/s
Measurement	2 Pirani pressure gauges + power supply 2 Penning pressure gauges + power supply 2 Bayard Alpert pressure gauges + power supply

Table VII-5: vacuum systems for the linac and the medium energy line

VII.4.2.3 Vaccum systems for the high energy line
Required pressures

The average pressure in the high energy lines is 1 x 10^{-5} Pa.

Vacuum chambers

The vacuum chambers are made of stainless steel, as for the synchrotron. The junctions are made using Conflat® flanges and with copper seals.

Vacuum and measurement devices

Table VII-6 below summarizes the main characteristics of the pumping system for the high energy lines. Immediately next to the synchrotron exit point, a high-speed valve is placed as a safety device. Each line has its own pre-evacuation and pumping system. The pressure measurements and safety functions are dealt identically to those in the rest of the machine.

VII-5
Accelerating system of the synchrotron

Pre-evacuation	4 dry mechanical pumps (15m^3/h) 4 turbomolecular pumps (150l/s) 4 Pirani pressure gauges + power supply 4 Penning pressure gauges + power supply 4 x CF 100 isolating valves for the TMP
Pumping	8 ion pumps 150l/s 2 ion pumps 400l/s 4 x CF 100 isolating valves for the sections 1 x CF 100 high-speed valve
Measurement	4 Pirani pressure gauges + power supply 4 Penning pressure gauges + power supply 4 Bayard Alpert pressure gauges + power supply

Table VII-6: vacuum system for the high energy lines

The acceleration of protons and light ions in a synchrotron from a few MeV/amu up to energies of a few hundred MeV/amu requires the development and implementation of a radio frequency cavity which can be tuned across a wide frequency range: a few hundred kHz to a few MHz [32]. Until very recently (1990) these cavities used ferrites as the electromagnetic load. The main characteristics required for these materials are naturally a high magnetic permeability and low electromagnetic losses. The power of the associated amplifiers is several dozen kW. Of course, the operation of these cavities has been improved with successive developments of proton and heavy ion synchrotrons, and a large number of radio frequency configurations have been used.

Requirements for increasingly compact machines are now appearing, in particular for accelerators for medical use. Considerable progress has been made due to the use of amorphous magnetic materials. These materials have a very high magnetic permeability at low frequency so that the longitudinal dimension of these cavities is smaller than that of a ferrite loaded cavity. Moreover, these materials allow a greater deviation of the tuning frequency of the cavity. The polarization circuits of the material are also simplified [33] [34].

The cavity proposed for the ETOILE project is identical to that proposed in PIMMS and in the CNA project. It is based on a prototype using the materials already mentioned, which was tested in 1987 at the Saturne National Laboratory, then transferred to CERN. The configuration used is the combination of 2 quarter wave lines in opposition, separated by the accelerator gap. The polarization of the material only requires a maximum of a few dozen amperes to cover the frequency range (0.5 MHz – 4 MHz).

The associated power amplifier has a push-pull structure. The cavity has already been tested by coupling it to a 2 tube amplifier (each tube can deliver a power of 50 KW [35]).

The day-to-day operation of a synchrotron for medical use must be as easy as possible. For this reason it is planned that the "low level" electronics associated with the radio frequency system of the synchrotron will be mainly integrated in the control system of the facility. Interfaces with operators will therefore be made extremely user-friendly. The parameters and their evolution will thus be displayed and any malfunctions detected immediately.

VII-6 Diagnostics

The large amount of equipment planned for ETOILE is necessary to ensure reliable operation in an industrial type frame, in which operation of the machine must be highly automated. The diagnostics are totally integrated in the control system, and thus also have a user-friendly operator interface. The diagnostics include both the systems necessary for day-to-day operation and those required for specific "machine" measurements. The fact that a person is being irradiated imposes strict requirements in terms of safety. It is also essential to ensure that the prescribed dose is given, as well as its location.

The operation of a synchrotron which is for medical use only requires a wide range of beam diagnostics to perform the following functions:

- start up the accelerators and bring them quickly up to nominal performance,
- check the beam characteristics in order to qualify it prior to use for medical treatment,
- measure and log the beam parameters to guarantee reliability and traceability of operation,
- detect malfunctions and quickly ascertain the cause.

Measurements which are essential for operation concern:

- the intensity of the beams and thus measurement of the transmission efficiency of the beam transport lines and the machines,
- the position of the centre of gravity of the beams. This measurement is essential for the automatic alignment of the beam on its nominal axis,
- the transverse profiles of the beam.

Beam intensity

The intensity of the beam is measured from the ion sources up to the synchrotron exit point using current transformers giving its AC and DC components.

For the lines to the treatment rooms, the absolute intensity is measured using Faraday cups, which are interceptive diagnostic devices. These are used to calibrate secondary emission chambers, which are non-interceptive, and can remain inserted in the beam during operation. They also provide the image of the spill. Real-time control of the beam is thus provided.

Position of the beam centre of gravity

Stripline electrodes for measuring the position of the beam centre of gravity are installed in the injection line from the linac up to the synchrotron. A precision of 1/100 of the diameter of the vacuum chamber can be achieved. Automatic alignment of the beam can be achieved using an appropriate operating program.

The synchrotron is equipped with pick-up electrodes which are essential for measuring the closed orbit and for measurements specific to synchrotrons, such as the tune number. This type of electrode will also be used for measuring the beam transfer function.

In the high energy lines the position of the beam is measured by multiwire ionization chambers which also give the beam profiles. These are the only detectors which can be used here.

For the treatment rooms, multiwire ionization chambers will be used whose high voltages and gas pressure can be fully controlled. These devices are essential to guarantee the characteristics of the beam up to the patient.

Transverse beam profiles

In the low energy line upstream of the linear accelerator, it is necessary to use profilers to determine the characteristics of the beam before it enters the radio-frequency quadrupole and the synchrotron. The technology for the detectors to be developed is known [34]. For the synchrotron, a residual gas ionization profiler needs to be developed.

In the high energy lines, the profiles are given by multiwire ionization chambers.

Note: diagnostics are constantly being developed and will be updated in line with future technical developments.

.

Location/function	Type	Quantity
Injector, low and medium energy lines		
Beam display	Scintillators + C.C.D cameras	8
Beam intensity (D.C. component)	D.C. Current Transformer	3
Beam intensity (A.C. component)	A.C. Current Transformer	3
Measurement of number of charges	Faraday cups	5
Beam transverse profile	Profilers	8
Position of the beam centre of gravity	Stripline pick-up electrodes	5
Beam phase / RF / energy	Capacitive pick-up electrodes	4
Shaping of beam	Horizontals and vertical slits	5 horizontal + 5 vertical
Synchrotron		
Beam display	Scintillateurs + cameras C.C.D.	2
Position of the beam centre of gravity	Electrodes "pick up capacitives"	10/8 (horizontal/vertical)
Beam intensity (D.C. component)	D.C. Current Transformer	1
Beam intensity (A.C. component)	A.C. Current Transformer	1
Beam phase / RF	Electrodes "Pick up capacitives"	1
Transverse profile of the circulating beam	Moniteur à ionisation du gaz résiduel	1 (horizontal/vertical)
Beam loss monitor	chambre à ionisation	10
Beam transfer functions	Déflecteurs électrostatiques	2 (horizontal/vertical)
"Schottky" diagnostics	Electrodes "pick up capacitives"	2 (horizontal/vertical)
High energy lines		
Beam display	Scintillators + CCD cameras	9
Beam intensity	Faraday cups	5
Beam transverse profile	Multiwire ionization chambers	22
On-line beam control	Secondary emission chamber	4
Beam loss monitors	Ionization chambers	10
Treatment rooms		
On-line dose control	Ionization chambers	15 (3 beam lines)

Table VII-7: summary of the beam diagnostics planned for the ETOILE project (including treatment rooms)

VII-7
Systems for distribution of the dose to the patient

VII-7-1 Active scanning

An active system for distribution of the dose can be installed in a room with fixed beam (horizontal or vertical) or in a room with gantry.

Beam scanning equipment has been developed for carbon beams at GSI and for protons at PSI (Switzerland) with the aim of developing conformal treatment of tumours.

The active scanning system [37] will be similar to that developed by GSI and proposed for the HICAT project [38]. It is placed downstream of the last deflection dipole. This makes it possible to considerably reduce the size, and thus the cost, of the optical elements. This is also a definite advantage in terms of handling (see also the "beam distribution" section). However, it also means that the line with vertical beam has to be higher.

The energy of the beam, which can be well controlled, precisely defines the depth of the Bragg peak for a given spill.

The corresponding section will be scanned using two magnetic dipoles, and dose modulation can be obtained by varying the scanning speed (which can reach 10 m/s). The dose will be controlled in real time, as stated previously, in order to compensate for any fluctuations. The synchrotron allows to interrupt irradiation during a spill in order to avoid irradiating healthy tissue located between two non-connected parts of the tumour and to minimize the treatment time. In this way, it is not necessary to start a new machine cycle.

Once the section has been fully irradiated, the depth of treatment will be changed by changing the energy of the beam delivered in the next cycle.

Using this scanning technique, shown in figure VII-2, it is therefore possible to scan all the layers and follow the contours of the tumour with an extremely high degree of precision.

Table VII-8 gives a few typical specifications of the scanning system [38]

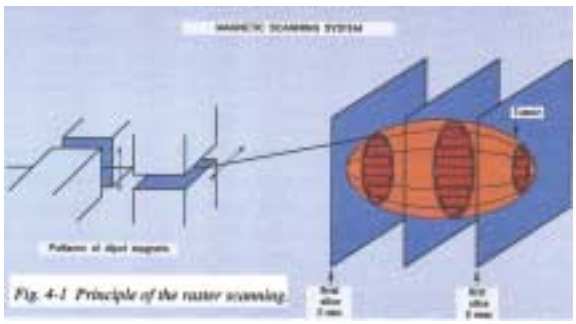


Figure VII-2: principle of the active system (irradiation by scanning). GSI doc. [6]

Parameters :	Horizontal scanner :	Vertical scanner :
Maximum magnetic field	0.38T	0.38T
Sweep rate	38 T/s	10 T/s
Maximum bending angle	1.45°	3.3°
Magnetic length	0.546 m	1.220 m
Aperture	140 mm x 130 mm	170 mm x 170 mm
Maximum current	400 A	400 A
Conductor cross-section	8.5 x 8.5 mm	8.5 x 8.5 mm
Number of turns	96	128
Power consumption	11 kW	25 kW
Weight	275 kg	725 kg

Table VII-8: characteristics of the scanning magnets

VII-7-2 Passive mode distribution

Although the "active scanning" method is the irradiation technique planned for the ETOILE project, the possibility of "passive" irradiation, as used for example at the HIMAC synchrotron at Chiba [39], should be allowed for. The beam and the optical elements of the transport lines at the facility must also be suitable for the use of this technique.

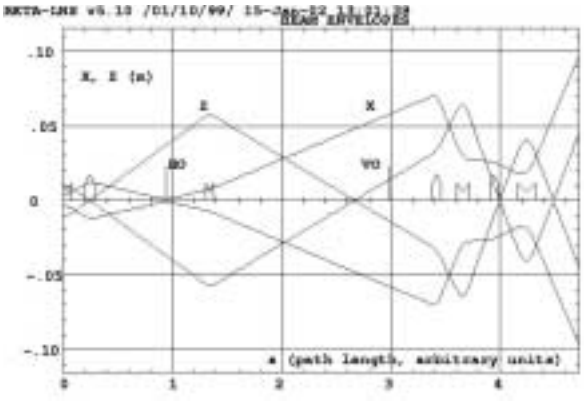
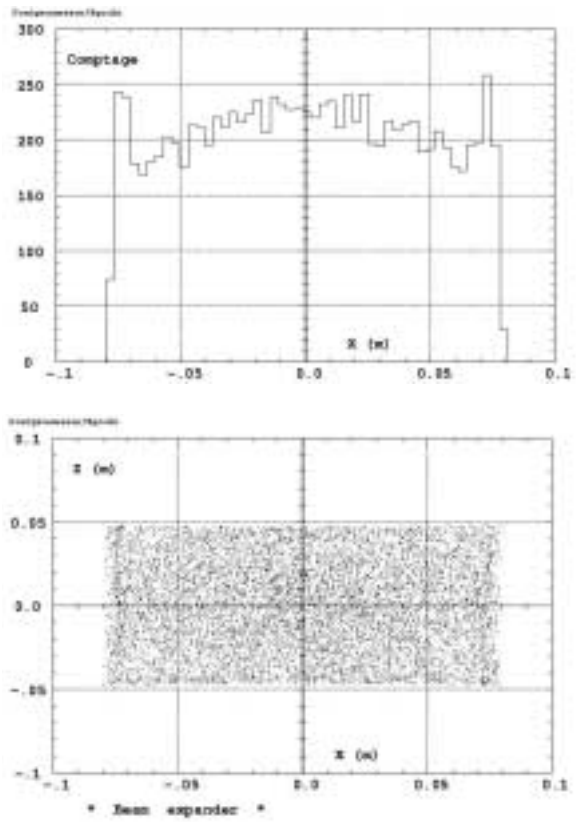


Figure VII-3: main optics of a disperser-uniformizer combined with the high energy lines. The main feature of the device is the insertion of two non-linear magnetic lenses (octupoles, HO and VO)



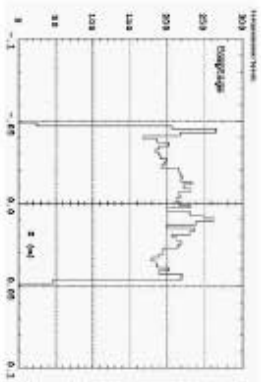


Figure VII-4: section of the beam with almost uniform transverse density obtained by means of octupolar lenses

The properties of the beam delivered to the patient in the case of the passive irradiation technique are obtained by degradation of the incident beam characteristics supplied by the accelerator downstream of the high energy lines. To do this, position and/or energy dispersion devices are used, combined with conformation devices which are either lateral (collimators) or distal (compensators).

Position dispersion expands the transverse dimensions of the incident beam. It is achieved for example by scanning the incident beam (wobbling). Two-dimensional conformation to the geometry of the area to be irradiated is carried out using devices such as asymmetric collimators or multileaf collimators.

Energy dispersion or distal dispersion enables SOBP (Spread Out Bragg Peak) which spreads out the depth of the irradiated area. This effect may be combined with modification of the average energy of the beam in order to adjust the irradiated depth. Distal conformation to the volume to be irradiated is obtained using devices such as a transmission block or compensator bolus.

It should be noted that devices for dispersion-uniformization of the transverse density, which are purely optical and thus not interceptive, seem to lend themselves to use in hadrontherapy. This type of device, for which the principle of use is shown in figure VII-3 [40], has already been studied in other projects [41].

• VIII •

Control system. Computer infrastructure

This section covers all the elements needed for the facility in terms of the control system, equipment for general computing and data storage, networks and operation of the facility. The following section is designed to provide the basic elements needed to carry out the detailed design of the control system. Where possible, commercially available components which meet the requirements are indicated. However, in view of the rate of industrial development in this field, it is clear that the choices made here will have to be updated at the construction stage. They do, however, demonstrate the feasibility of the technical options chosen. We also make reference to [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53].

VIII-1
Overall design

The system described in this section can be divided into two main parts:

- The accelerator control system, responsible for supervising the accelerator from the source up to the end of the transfer lines. The "accelerator" staff will use this control system from the main control room.
- The treatment control system, responsible for supplying the correct dose rate to the patient. This system must control in particular all the safety aspects concerning the patient. The medical staff will use this system from dedicated control rooms.

The above subsystems will be linked together by a standard Ethernet network.

The number of nodes (PC, VME, workstations, computer, other) to be connected to the network has been estimated for each part of the facility :

- Accelerator: 70 nodes
- Machine and treatment control rooms: 50 nodes
- Offices: 80 nodes

Each node will be connected to a switch by a point-to-point link. Two switches would seem to be sufficient for this facility. These switches are available from CISCO, for example, in various configurations (CATALYST family). They provide connections with speeds ranging from 10 Mbps up to 1 Gbps. VLAN technology is used to isolate the logical networks. This technology groups individual nodes into logical groups whatever their geographical position on the network.

One VLAN will be used for the accelerator, one for the treatment rooms and one for the offices.

It will be possible to access the Internet via a dedicated node running firewall software to protect the site from external attack. One of the leading products in this field is FireWall-1 from CheckPoint.

VIII-2
Accelerator control system

This concerns the source, the injector, the synchrotron and the beam lines up to the treatment rooms. Its purpose is to adjust the various parts of the machine, monitor the parameters, manage the safety devices, provide the interface with the operators, and carry out the essential function of pulse-to-pulse modulation of the parameters for adjusting the energy, the beam diameter and the intensity at the patient.

The system is based on established solutions: VME will be used for interfacing the equipment, with the possibility of using VXI for controlling the RF system.

For high level tasks, such as the operator interface, database management or archiving, workstations with various configurations will be used. A TCP-IP network will link the various elements.

At the lower level, fieldbuses will be used, such as: G3 [44] for the optical loops for the source, GPIB for the RF instrumentation, Worldfip or CAN or Profibus for the power supplies.

The control software will be EPICS [45], one of the most widely used in the field of accelerators. This software will constitute the top layer of the vxWorks real-time system [46]. This architecture is illustrated in figure VIII-1.

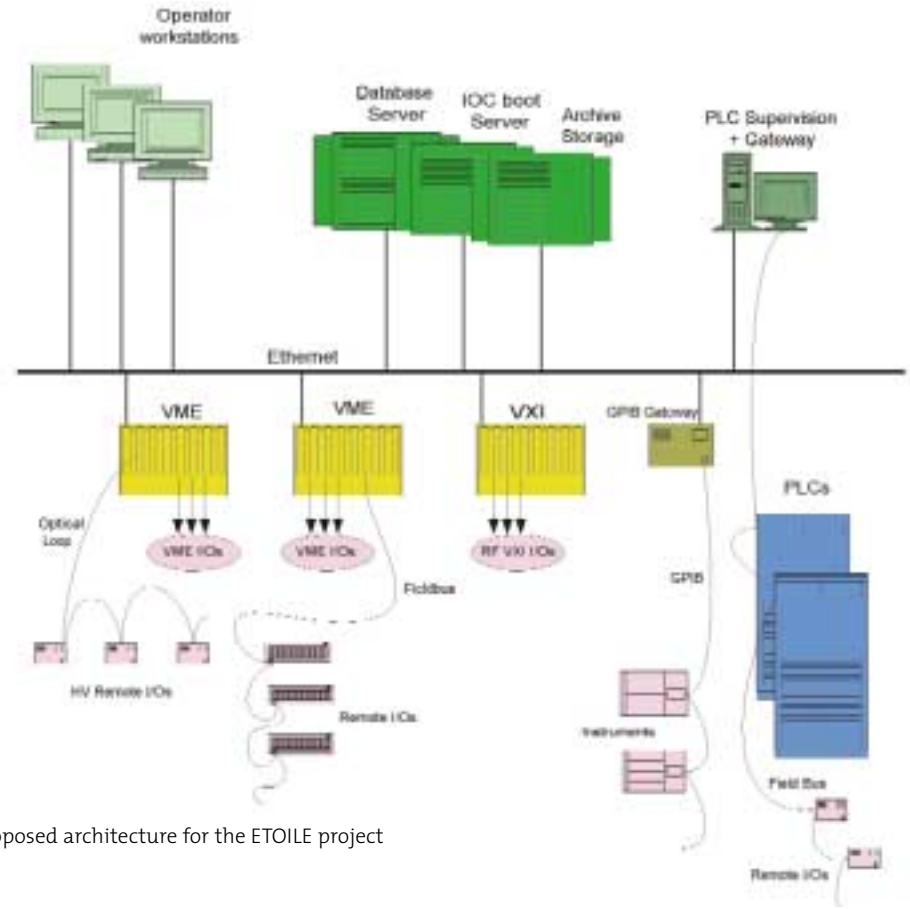


Figure VIII-1: proposed architecture for the ETOILE project control system

This system meets the following requirements of the specification.

• Reliability

"The hardware and software chosen must ensure a good level of reliability. The day-to-day operation in a hospital environment rules out any solution which may present risks".

VME is a very robust mechanical and electronic standard which is used in harsh environments: TGV train, Pathfinder Mars rover.

Servers and workstations which are critical for the operation of the machine will be equipped with redundant power supplies and RAID disks to improve their reliability.

EPICS and vxWorks are well known for being reliable software components.

This architecture (VME + workstations + vxWorks) has been successfully used, for example, for more than 10 years at the CEA Saclay. CEA Saclay also uses EPICS for various projects at DESY, TJNAF and CERN.

• Robustness

"The system must provide protections to avoid any catastrophic consequences for treatment or for the accelerator which may result from human error. Temporary failure of any of the control systems must have a limited impact. Such a failure must at minimum leave the accelerator in a condition in which its operation remains possible".

Following the technique used at GSI and planned for the future at Heidelberg [47], the various possible adjustments of the accelerator will be stored locally in the VME system in Flash-EPROMs. This will avoid the risk of adjustment values being changed accidentally, as could happen if these values were stored in computer files, for example.

Before a treatment is started, the accelerator must be protected against any accidental change made by the operators. This locking mechanism is necessary. For this purpose, EPICS provides a very powerful secure access structure. Permission for an operator to access a parameter is subject to a combination of conditions which may be: identification of the person requesting access, of where the request originated, what action is to be performed, and (particularly important here) in what context.

In this architecture, there is no data concentrator or any other system which could have catastrophic consequences if it failed. EPICS could be described as being somewhat fault-tolerant.

The latest version of vxWorks provides memory protection.

• Availability

"Intelligent tools must enable the operator to detect and quickly locate any problems. The modular hardware architecture must enable rapid replacement ".

The EPICS general alarm detection tools will be used to inform the operator of any faulty channels.

VME technology enables a module to be replaced in less than a minute. The restart of a VME crate takes less than a minute.

• Safety

"The safety of people and equipment requires the use of standard computer systems".

This point concerns the safety of the accelerator itself (beam losses, cooling default, temperature rise in the power supplies, etc) and the safety of staff (for example, access to rooms which may receive the beam). These safety aspects are now commonly handled using PLCs in a redundant configuration.

• Performance

"This requirement concerns the particular requirements connected with pulse-to-pulse operation".

A specific network will handle rapid synchronization problems. The control system responsible for ramping the radio frequency or the magnets will be chosen accordingly (use of fast DSP).

The EPICS protocols and databases will be optimized for maximum performance.

• User friendliness

"The tools for interaction with the control system must be intuitive and easy to use".

Several features of EPICS will have to be improved to meet this requirement.

• Support

"Each hardware and software component must have the support of large industrial companies or a large group of users".

VME components are produced by well-established commercial firms, and EPICS also has the support of the accelerator communities throughout the world.

14 VME crates will be used to control the machines (sources, linac, synchrotron). Some of these crates will be to standard VXI for controlling the radio frequency.

10 VME crates will be used for beam transport to the treatment rooms. The number of crates has been chosen to reduce the length of the cable runs (typically, one VME crate will control 2 dipoles).

For local maintenance a number of workstations will be installed along the accelerator: 9 for the sources, linac, synchrotron, and 4 for the beam transports.

VIII-3
Treatment control system

The following functions are required:

- Selection of the treatment plan from the patient's database
- Request to the accelerator control system in order to obtain the beam characteristics corresponding to this treatment plan
- Adjustment and control of the scanning magnets
- Control of the intensity and position of the beam
- Stopping/starting the beam according to the progress of the treatment
- Interfacing with the medical operators
- Archiving of all useful information concerning the treatment

A number of the choices made for the accelerator control system will be used: VME for the hardware interfaces, workstations for the operator interface, Ethernet for the communication requirements. Many of the characteristics concerning reliability, robustness and availability will therefore be valid.

The treatment control system is organized as follows, and is shown in figure VIII-2.

• Supervision

This task will be performed by a VME crate containing a CPU running under EPICS which will be linked to the accelerator control system via Ethernet. This will display the current treatment, send the necessary requests to carry out the treatment, and provide all the information to the medical console. This system will also be responsible for the centralized management of the parameters.

• Sequencer

A second CPU will be responsible for sequencing all the operations specified in the treatment plan. In order to ensure maximum safety of this sequencer, which is crucial for treatment, it will not run under EPICS, and will not be connected to the Ethernet. The software will be resident in rewritable memories (EPROM), and the interface with the supervision and acquisition systems will be via shared VME memories.

• Acquisition

A fast acquisition system will play a number of important roles in the sequencing and carrying out of treatment.

This system sends requests to the accelerator control system concerning the required beam characteristics. It also controls the scanning magnets. It must acquire important parameters supplied by the ionization chambers, such as the position, intensity and profile of the beam.

If an anomaly is detected, it must send an alarm to the safety system very quickly. It must therefore be very fast, and like the GSI choice for this, a DSP-based architecture will be used. These processors can read the treatment electronics of the ionization chambers via a dedicated channel at 20 Mb per second.

A system grouping up to 4 DSP with 4 communication channels in one VME crate is sold for example by Pentek [48]. This crate will give a procedure stop signal if one of the above parameters (scanning magnet, intensity, position) moves outside the specified tolerances. A specific alarm signal will also be produced in the event of failure of one of the DSP.

The planned configuration provides adequate redundancy to ensure a good level of safety for the system.

• Hard-wired safety systems

The purpose of this crate is to provide the maximum possible level of safety to the patient. It receives various signals, analyzes them and generates an output signal enabling or inhibiting the use of the beam. To obtain the highest possible level of reliability, a solution based on a completely hard-wired system will be used. The signals coming to this crate are from the DSP, the operator console, and from various alarms at the patient.

• Manual medical console

This console is completely hard-wired and will be used mainly by the medical operators to start treatment, send a fast stop signal and to display the treatment parameters on appropriate LED display units. If the medical workstation or the VME dedicated to treatment fails, this manual console will remain operational, thus providing a high degree of safety.

• Medical workstation

This workstation has a very sophisticated graphics interface to display and store data for the patient treatment plans. It also gives the status of the critical components in the facility: magnets, ionization chambers, patient positioning, high voltages. It displays all the alarms detected by the safety systems.

Another screen will display the tumour being treated with the possibility of zooming in on the part being irradiated. It stores the whole treatment on disk, which can then be used for subsequent analysis. The graphics package IDL [49] is ideal for this purpose.

Each treatment room will have a VME assembly (safety crate, manual console, and workstation) with the corresponding software.

This treatment control system, although limited in terms of the hardware used, is by far the most complex and crucial part of the whole facility.

In particular all aspects concerning safety, reliability, redundancy, user-friendliness and ergonomics of the system must be carefully designed and developed, as well as being inspected and audited by external organizations.

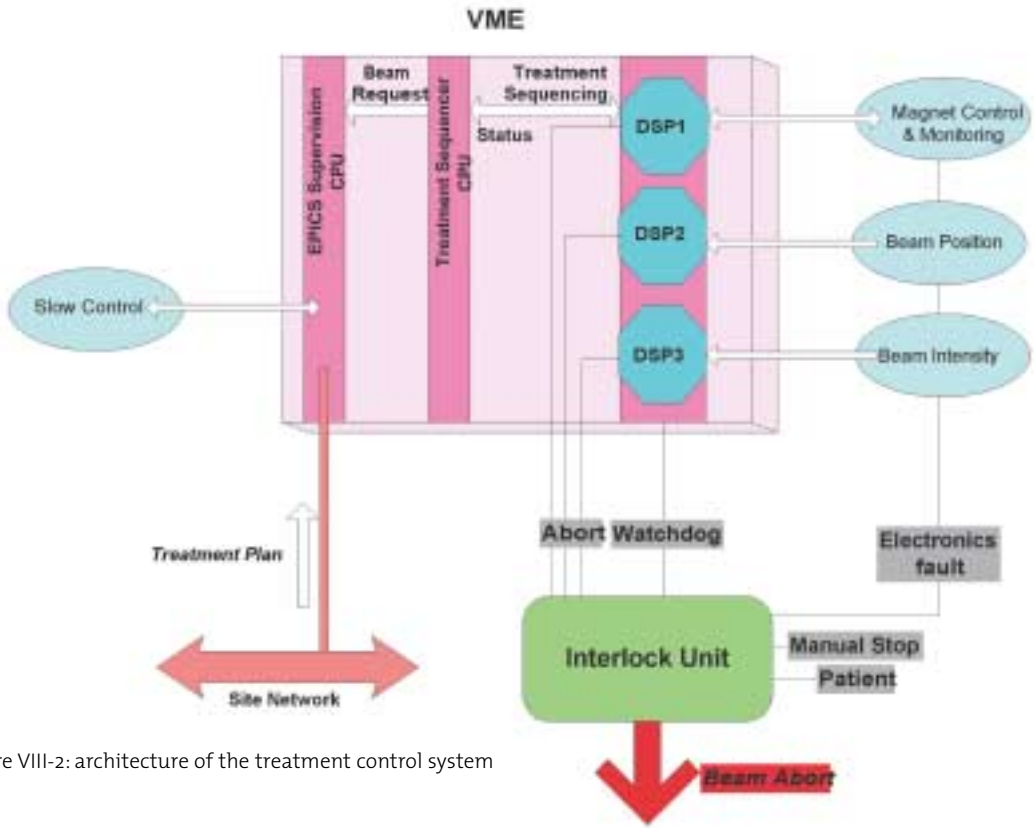


Figure VIII-2: architecture of the treatment control system

VIII-4
Computer infrastructure

• Computers running under UNIX/LINUX

These will be used for the following purposes:

- accelerator database server: A commercial ORACLE [50] type database will be used to describe all the equipment (configuration management). The real-time data to be loaded in the VME will be extracted from this database.
- treatment database server: Another ORACLE type database will contain all the information concerning patients and their treatment. For an assumed 1000 patients per year, this will represent a significant volume of stored data.
- archive server (traceability): This computer will continuously archive all the parameters of the facility, so that, if required, these parameters can be correlated with a particular treatment.
- other smaller servers will be used, for example, for storing VME startup programs or for development purposes. A mail server and an Internet server will also, of course, be necessary.

• High volume storage and backup

All the servers will have sufficient storage capacity. However, to provide a greater storage capacity, smooth evolution and maximum availability, an NAS (Network Attached Storage) storage unit is planned. This unit will provide up to 1 Tbyte of storage. A central system will carry out server backups. A robotized tape library, such as the P6000 from ATL [52] with Netbackup software from VERITAS [53], may be used.

In addition to daily backup operations, this will provide long term storage for treatment data.

• IX •

Testing the beam quality

To ensure the quality of the treatment using carbon ions, the beam which is delivered must be qualified. For one patient, the energy and intensity vary from spill to spill, at an approximate rate of 0.5 Hz. The beam which is delivered must have the required characteristics and a high level of stability, throughout the day, without the necessity for further adjustment phases. In addition, the dose deposited in the target volume must be totally guaranteed.

The assumptions made and the scenario used in this section are based on actual experience from GSI. At the start of the day a period of two hours is planned for quality test runs of the machine and the control system in each of the rooms [54]. A one-hour period of post-treatment checks is also planned at the end of the day [27] [54]. This period is a safety element.

IX-1
Testing the machine quality

The machine adjustments will be carried out at the end of the fishbone.

The energy of the beams delivered is guaranteed by means of Bragg peak measurements. The purity of the beam delivered and its intensity is also controlled.

The geometric precision of the beam (diameter and position) at the patient must be better than 1 mm to be able to guarantee the value, the uniformity and the location of the dose deposition. Experience of operation at GSI has demonstrated that this type of machine had a ± 0.5 mm drift over two weeks in the horizontal plane and was even better in the vertical plane. It also demonstrated that the theoretical "machine" parameters (voltage setpoints, current setpoints, etc), stored in the memory, were sufficiently reproducible and reliable.

IX-2
Testing the quality of treatment and real-time control at the patient

Qualification

For a reference machine configuration, the real-time dosimetry diagnostics, placed in the beam in front of the patient (Table VII-7), will be calibrated using calibrated ionization chambers. For this calibration, reference ionization chambers are placed in a volume of water. As in conventional radiotherapy, the reference measurement systems (ionization chamber, cable, electrometer) are calibrated by an approved central calibration laboratory.

For a given treatment, a set of measurements must first of all be taken on a water phantom to validate the machine configuration. Measurements can also be taken using solid phantoms (plastic plate type) and parallel plate ionization chambers (PPIC) and multiwire plate chambers (MWPC).

Development is currently being carried out on polymer gels to provide 3-D mapping of the deposited dose. It will be possible to transpose these techniques to conventional radiotherapy.

Figure IX-1 gives an example of measurement with a solid phantom [37] [55] consisting of a stack of several ionization chambers and plastic plates (PMMA) of variable thickness.

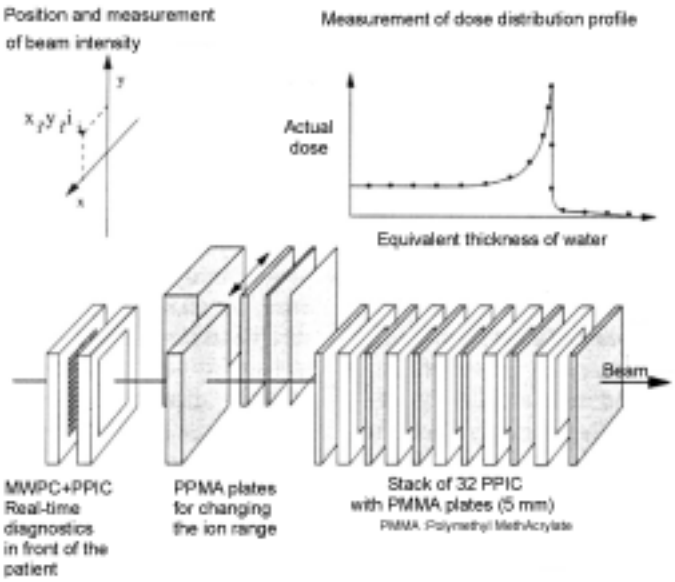


Figure IX-1: measurements on solid phantom

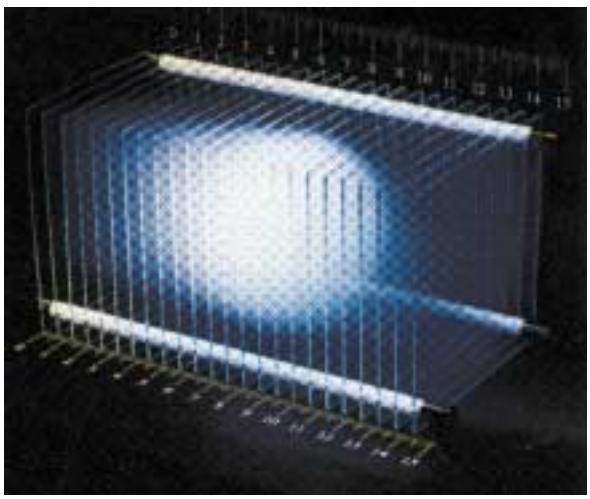


Figure IX-2: display of the 3-D distribution of the dose deposited in a reference material using dosimetric gels (from GSI [6])

Real-time dose control at patient level

During treatment, on-line control and control at patient location will be carried out using a series of wire chambers (profile measurement) and a series of ionization chambers (control of the intensity and the dose).

The dose deposition can be guaranteed by a measurement every 25 μs (as at GSI) during the scanning process. As already mentioned in the "beam scanning system" section, the area to be treated is scanned with no interruption in the spill, but the scanning speed is not constant. The beam is only moved from place to place after the prescribed dose has been reached.

• X •

Safety

The purpose of this section is to examine the radiological protection to be implemented around the facility which is to deliver proton beams to the patient with a maximum energy of 250 MeV (1×10^{10} particles per spill) and carbon ion beams with a maximum energy of 400 MeV/amu (4×10^{8} particles per spill). The case of beams of ions with an intermediate mass has also been included. The layout of the chicanes is given for information only in plan XVI-9 and is still to be finalized.

The hadrontherapy centre must meet the requirements of the regulation ensuring correct organization of the radiological protection for the staff working there and also for the environment and the public.

The main problems which arise are:

- the identification of controlled zones
- the determination of biological protections
- control of access in the rooms and around the rooms equipped to receive the beam
- the measurement of the dose equivalent rates connected with ambient radiation during operation of the accelerator and irradiation of patients
- the evaluation of constraints related to the radiologically-induced activation of the elements of the machine, air and water
- the handling of activated materials

X-1
Controlled zones

The radiological protection zoning based on operation of the machine is defined as follows:

- "machine" areas : forbidden access controlled zone
- areas accessible to patients : public zone (a dose equivalent rate of 0.5 μSv/hr is considered, applying the specification of 1 mSv/year for 2000 hours of presence [56])
- patient treatment areas : either forbidden access controlled zone (treatment in progress) or green controlled zone
- technical area on first floor: basic controlled zone (a dose equivalent rate of 10 μSv/hr, is considered, applying the limit of 20 mSv/year specified by European directive 96/29 for 2000 hours of presence)
- source room : basic controlled zone
- "living area" on first floor : public zone

During normal operation, losses are divided over 7 locations, as shown in plan XVI-9.

The main protection against radiation will be the thickness of the shielding walls.

The beam losses are defined in Table X-1 [56] and diagram XVI-9.

Loss points	number of ^{12}C per spill [3]	number of protons per spill[4]
P1 (extraction)	6.4×10^{7}	1.6×10^{9}
P2 (adjustment line)	5.76×10^{8}	1.44×10^{10}
P3 (scanning: treatment room)	1.32×10^{8}	3.31×10^{9}
P4 (patient irradiation)	4×10^{8}	1×10^{10}
P5 (scanning: treatment room)	1.32×10^{8}	3.31×10^{9}
P6 (patient irradiation)	4×10^{8}	1×10^{10}
P7 (patient irradiation)	4×10^{8}	1×10^{10}

Table X-1: losses (active scanning)

It should be noted that the intensity of protons is always 25 times greater than that of ^{12}C.

The calculations performed by the radiological protection department of CEA Saclay [56] have given the following results for the thickness of passive biological shielding (concrete density 2.3) to be installed in order to comply with the radiological protection objectives.

[3] spill frequency: once every 1.5 s
[4] number of protons in active mode

Wall	Distance between source and observer (m)	Loss(es) in question	Angle in relation to the beam (°)	Thickness required (cm)
ME	10.60	P1	90	90
MN	20	P1	0	200
	6.4	P2	90	200
MO	5	P2	0	500*
	6.4	P7	90	200
MS1	13**	P7	0	380***
MS2	13**	P3+P4	0	380***
	13**	P5+P6	0	380***
MS3	26	P1	90	70
MSA	6.4	P3+P4	90	200
	6.4	P5+P6	90	200
MSN	3	P2	90	150
Plafond	3	P3+P4	90	150

(*) : local protection should be considered (beam stop)
(**) : distance from source to start of baffle (living area side)
(***) : total thickness of front walls of the baffle

Table X-2: thickness of biological shielding

At 0°, the ^{12}C require a thickness of 360 cm for the facility. At greater angles it is sized for protons. At 90°, the facility must be totally sized for protons.

Sky effect has been taken into account in the determination of the thickness of the concrete slab above the irradiation areas. It appears that for a dose equivalent rate taken at 10 µSv/hr on the roof, the sky effect does not cause any higher exposure level than the public dose at a distance from the facility. The final engineering study will determine the thicknesses of concrete walls that sustain machine elements and the concrete floor above the synchrotron. These thicknesses will be larger than required for radiation safety.

X-2
Systems for stopping the beam in the event of an anomaly

This involves the "beam safety devices" (SF). Their operation will be essential in the event of any anomaly and each time there is a request to enter a room whose access is controlled.

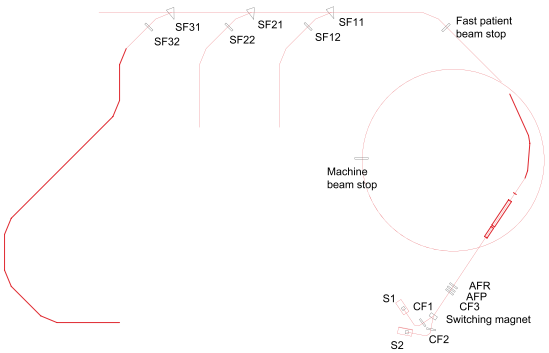


Figure X-1: location of the beam safety devices

Area of application	Conditions
Machine room	2/3 entre CF1, CF3 et HF S1 2/3 entre CF2, CF3 et HF S2
Room 1	SF11 et SF12
Room 2	SF21 et SF22
Room 3	SF31 et SF32
On-line source	Diversion (direction of magnet)
Main beam stop (AFP)	Activated by the main system if there is an access or radiation detection fault and if the SF are not in place after 2 seconds
Redundant beam stop (AFR)	Activated by the redundant system if beam is present and presence of persons detected and if the SF are not in place after 2 seconds
Fast beam stop	Protection of the patient in the event of an irradiation fault

Table X-3: beam safety devices

There are beam stopping devices which can be inserted along the transport line in order ensure that it is not possible for the beam to enter a room in which staff are present. There is also a beam stopping device enclosed in a special concrete block located at the end of the fishbone. The role of this device is to enable adjustment of the beam intensity. A fast beam stop (200 microseconds) is planned for the first deviation after ejection of the beam from the machine.

X-3
Access control

This involves access to the rooms which may receive the beam. Two situations need to be considered: treatment room and machine room.

When the beam safety devices for the treatment room are in place, the room is a monitored zone with free access. When the patient has been positioned, the person responsible for the irradiation will carry out a check, leave the room and close the door, then confirm a "ready" to carry out irradiation (release of the beam safety functions and sending the beam). Staff access to the treatment room will be authorized as soon as the beam is no longer arriving on the patient (fast setting of the beam safety devices). This authorization will also depend on the neutron radiological level given by the indicator for the room.

The machine room will be accessed via an intermediate chamber which will make it possible to count and/or display the movement of staff. The assurance that there is no-one in the room when the beam safety functions are released will be conditional upon initialization of the counting system after a check has been carried out, if necessary. Visual and audible devices will be used to warn workers inside the rooms of the radiological level and that the beam is due to arrive. It will only be possible to open locked doors from the outside using a badge or an emergency key. Unexpected opening of a door will trigger the setting of the beam safety devices.

The access management system will use safety PLCs to control the opening and closing of the treatment room doors and the doors of the intermediate chambers, and also to perform the counting functions.

The radioactivity levels will be monitored by a set of fixed and mobile indicators placed at appropriate points over as large an area as possible. The radiological protection indicators connected to an illuminated signaling system will authorize or prohibit access to the synchrotron room, to the beam line and to the treatment rooms, and will provide information on the activity in these different areas. These sets of indicators will be connected to a central control panel which will provide information on the status of the various detection assemblies and the dose rate value measured at the position of the detector. All the data will be archived by the control system.

The beam safety devices will be controlled by two independent systems. The main system will monitor the levels of radiation and control access to the rooms. The redundant system will monitor the status of the beam safety devices and any access and will manage the risk of presence of the beam in a room in which staff are present.

X-4
Measurement of radiation

For this type of facility, 5 neutron indicators are recommended, located as follows: one per treatment room, one in the public area, one in the controlled zone in the technical area.

In addition, it is advisable to provide 5 photon indicators for each of the beam loss points in order to control external exposure due to residual activation.

The thickness of the walls has only been calculated based on losses during normal operation. It would be advisable to check that the beam losses during the adjustment phases do not cause risks greater than those during normal operation.

• XI •

Building and infrastructures

XI-1
Civil engineering

The civil engineering will depend on the radiological protection studies which determine the thickness of the biological protections both for the side walls and for the slab located in the ceiling of the synchrotron (sky effect). It will also depend on the options examined: line with vertical beam or rotating gantry, for the installation of a traversing crane and the reinforcement of the floor slab. No detailed study of the concrete structures has yet been carried out.

A plan has been proposed (after studying comparable projects) for the layout of the machine devices and the medical and technical areas.

There is no traversing crane in the synchrotron room (unlike the area containing the vertical beam or a gantry) but a distance of 3 metres has been kept free around it for transporting the dipoles or other heavy equipment using an appropriate machine [55].

The fishbone structure of the beam distribution system will facilitate further development of the building.

In accordance with the specifications of the doctors, the reception area will be on the same floor as the treatment rooms and the machine. The patient's route has been designed so as to avoid meeting other patients, machine technicians, or research staff. An anesthetics room, combined with a recovery room, is also planned.

The upper floor of the building is designed to house the medical services (examination rooms, scanner and MRI) and the general and auxiliary services (electrical distribution, cooling, ventilation). It will also house all the power supplies in order to minimize their distance from the equipment.

The plans showing the different options for the facilities at the hadrontherapy centre are given in plans XVI-3 to XVI-7 (Plans of the treatment floor and the service floor, sectional drawings, solution with gantry and route for patients). In this initial design the building will occupy a ground area of 64 x 58 m^2. The synchrotron room alone will measure approximately 30 x 30 m^2.

XI-2
Infrastructures

These designs, developed in the context of a preliminary design, have taken into account, with the help of manufacturers, all the technical aspects and requirements of a medical treatment centre, in order to estimate the cost.

XI-2-1 Main power supply and uninterruptible power supply

The synchrotron is a pulsed machine. During the cycle, on increasing to the maximum field (operation at maximum energy and therefore at maximum power), the current in the dipoles varies from 100 to close to 3000 amperes in ~ 0.8 s. The voltage can therefore reach over 1000 volts, while its value at the plateau is around 200 volts. At lower energy, after the spill, it will be necessary to increase the current to maximum before decreasing it for the start of a new machine cycle, in order to maintain the same hysteresis cycle of the magnets. This causes a significant fluctuation in the active power (up to 2MW) and reactive power (up to 5 MVAR) on the mains supply, whose consequences would be perturbations of around 10% of the mains voltage if compensation were not provided.

In addition, thyristor power supplies generate low frequency harmonic currents[5] which cause perturbations on the mains supply.

It will therefore be necessary to minimize the level of this perturbation caused on the mains supply (voltage, reactive power and harmonics generated), so that it remains below that specified by the electricity supplier[6] and to avoid causing malfunctions in the facility itself. A system must therefore be provided to compensate for the reactive energy and to filter the harmonic currents.

[5] The dipole power supplies generate harmonics 11 and 13 (550 Hz and 650 Hz). This interference is proportional to the power, hence the need to filter them.

[6] The electricity supplier invoices its customers for the reactive energy consumed and prohibits them from producing harmonics above a certain level. The consumption of reactive energy is free of charge (EDF in France) if it is kept to:
$\tan \varphi$ = reactive power (kVARh) / active power (kWh) < 0.4
φ : phase difference between the current and the voltage
F Decre and H Chedeville. Principes de tarification de l'électricité en France. D4 023, traité Génie électrique, sept.1995.

As at CERN (SPS synchrotron) we propose the use of static reactive power compensators (known as "VAR compensators") which reduce the voltage perturbation and the level of harmonics to a level of 1%. This system consists of a bank of conventional filter capacitors (3-phase arms of inductances and capacitors in series) and an absorber, i.e. inductances controlled by a thyristor controller. The bank will filter harmonics 5, 7, 11 and above, and supply a fixed capacitive reactive power in order to compensate for the maximum reactive power of the facility. The absorber consumes a variable quantity of inductive reactive power, the variations of which are opposed to those of the loads (magnet power supplies) using a servo system. Thus the total reactive power of the facility remains constant.

This solution, which is consistent with the chosen power supplies, is proposed for the ETOILE project and has been costed with manufacturers. The compensation device must also have the same level of reliability as the machine.

Thyristor power supplies (low cost and simple to use) are very suitable for this range of power. Those chosen have a structure which minimizes the harmonic currents and consumes little reactive power.

The operation of the accelerator may be interrupted by a power failure or perturbation of a sufficient amplitude. The example of the ESRF (Electron Synchrotron Radiation Facility) demonstrates a sensitivity of 10% over the voltage of each phase if the duration exceeds 80 ms [57]. It is therefore essential as a priority, to:

- Back up data concerning treatments in progress, radiological controls, information related to the control system, access control, PET imaging.
- Protect sensitive equipment, such as the filaments of radio frequency tubes, the ion sources and the associated systems.

The time taken to restart operation must be limited to one hour, including testing, after restoration of the mains supply. This point has also been the subject of a consultation [58]. The solution proposed is a 250 kVA dynamic Uninterruptible Power Supply (UPS) with 15 seconds independent operation and return of power after a few seconds by a 300 kVA generating set.

A 1 MVA HQPS option (High Quality Power Supply: this is a diesel-driven generating set (started automatically in the event of a power breaks of more than a few seconds). It would ensure total continuity and keep additional elements in service, such as the cooling or air conditioning.

XI-2-2 Electrical distribution

The electricity supply is provided via 2 lines (main and backup) switched with a maximum trip time of 10 seconds. These lines end at a delivery unit located at the edge of the site. Two lines link the delivery unit to the distribution room located on the service floor of the building where there are 20 kV/400 V transformers [59]. The distribution and the isolation and protection devices make it possible to carry out maintenance work without disconnecting the whole installation.

Nine transformers have been planned for the supply of functionally and geographically consistent assemblies. These are all dry type transformers.

The low voltage electrical distribution separates the interruptible and uninterruptible supplies. Emergency stops are managed centrally by a PLC.

XI-2-3 Cooling

A specialist consultancy has been approached on this point [60]. The capacity of the demineralized water cooling plant for the accelerator and the beam lines has been cautiously estimated at 2 MW assuming continuous operation on a plateau at maximum energy. A pressure drop of 8 bars is assumed in the elements, which corresponds to a system pressure of 10 bars. The required inlet temperatures will be in the region of 20 °C, and the outlet temperatures will be 30 °C maximum. The average temperature of the elements will therefore be in the region of that of the machine room. All the pumps will be backed up.

Two solutions have been examined by the design office responsible for the costing:

- the first using the ground water from a bored well will meet the required conditions. It includes a buffer tank which will reduce the consumption of the water from the well and improve the operation of the temperature regulation.

- the second with a "wet" cooling tower, does not maintain the temperatures of the elements (26 °C and 41 °C) for a similar cost, due to the wet bulb temperature (21 °C).

The well solution is therefore recommended for its compliance with the specifications and for its reduced impact on the environment.

The installation has been divided into 4 circuits each with an exchanger, a demineralization circuit and relief pump. Part of the installation can, in backup operation, cool the ion source, part of the medium energy line and the filaments of the high frequency tubes.

XI-2-4 Handling

The installation of a traversing crane covering the synchrotron room over a 30 m diameter would have had considerable consequences in terms of the height beneath the ceiling and the direct and associated costs. The project has the advantage of only using small sized elements which are therefore of a moderate weight. The solution chosen for handling is that of the ESRF [57] : a low electric truck ("lobster") which travels around the ring and is capable of carrying a main dipole (weighing less than 8 tons). This requires that the high energy beam line can be disassembled on a length of approximately 4 m to allow the truck to pass. Local devices (hooked on special "rails" embedded in the concrete) will be provided for handling elements weighing a few hundred kilograms.

XI-2-5 Routes between the treatment floor and service floor

The power supplies on the service floor are located vertically above the corresponding elements (synchrotron, lines etc), which reduces the wiring lengths. The wiring is routed via cavities which provide protection against ionizing radiation.

XI-2-6 Electromagnetic interference

All the wiring will conform to standards. For example: installation in metal cable runs with few openings in a single layer, equipotential connections of cable runs and identical paths for connections to variable power supplies. There will therefore be no particular restrictions for patients with pacemakers for example.

• XII •

Restrictions related to the reference site

The altitude of the site chosen as the reference is between 193 m and 200 m. The highest altitude is located close to the ring road.

A number of restrictions can be observed from the zoning plans:
A project has been set up for the Vinatier site to be classified as a ZPPAUP zone (architectural, urban and landscape heritage protection zone). The Vinatier site is currently classified as a USP (palliative care unit)[7]. This zone is intended to cover sites for the location of the main general interest public amenities. All construction projects must take account of the functional and technical restrictions specific to that facility, its location and its role structuring the urban area, with links to the natural and man-made environment.

The Vinatier site is located in the "la Grange des Tours" area. The chosen plot on the Vinatier site includes a listed wooded green space (50 m strip along the ring road) and another preservation area in the centre of the plot.

A listed historical monument is located near the chosen site. This is the "maison Berliet" (39 avenue Esquirol in Lyon). The height of buildings is limited within a 500 m radius. According to the map showing public rights of way, the zone overlaps into the Vinatier site, but not the plot of the reference site [61].

An NGF altitude (NGF = French altitude measurement system) of 279 m (aircraft and clearance) must not be exceeded.

The zoning of the Neuro-Cardiogie/Villeurbanne-INSA microwave link does not overlap the zone of the Vinatier site. However consultations may be necessary in order to prevent interference.

The mapping of the natural level of radiological activity (zero point of the site) has not yet been carried out. It will be performed at different measurement points by an approved organization.

Climatological data have been obtained from Météofrance (French weather office). This data cover temperature, precipitation, air humidity and wind direction [62].

The drinking water supply and waste water collection networks have been obtained from the technical departments at Vinatier.

The solution for taking water from the ground water for the cold water source for the equipment cooling system is preferred (diagram XVI-10).

The electricity distribution company, EDF, has carried out a study for the supply of the necessary power from two different stations. The outline diagram of the electricity distribution is given in XVI-11).

Problems connected with lightning have been taken into account. The consequences of electromagnetic interference caused by equipment within the centre or outside the buildings must be examined.

7 Zoning regulations of the metropolitan authority of Lyon. Regulation dated 26 February 2001.

• XIII •

Treatment

XIII-1
Treatment plan

This subject, covering the hadrontherapy treatment plans is covered in volume I section V subsection 1.

XIII-2
Carbon ion hadrontherapy imaging

This subject, covering carbon ion hadrontherapy imaging is covered in volume I section V subsection 2.

XIII-3
Equipment of the treatment rooms and other associated areas

In accordance with the medical specifications, each treatment room has been equipped differently, but all future installations remain possible in line with developments in the technique, in particular for patient positioning and imaging. It will be possible to set up a passive dose distribution system in all the rooms in place of the active distribution system.

The systems for measurement of the doses deposited (ionization chambers), the robot-controlled systems for positioning the patient's bed or chair, the X-ray imaging systems and the laser or optical measurement apparatus are all identical, in order to minimize special training for hospital staff and maintain the uniformity and interchangeability of operations.

Optical systems installed in the treatment room will be used for additional control of all positioning operations (patient, bed, chair, water phantom and zero or resting point of the robot) with respect to those determined by laser beam.

Each room will be equipped with a support robot which can position a bed, a chair or a beam control device (phantom) in 6 axes (x, y, z, ρ, θ, ϕ).

As in conventional radiotherapy centres, it is intended that the patient immobilization systems will be made on site.

The patient pre-positioning rooms and irradiation control rooms will also have identical equipment.

In order to have access to all the necessary diagnostics before or after irradiation, an MRI scanner and an X-ray scanner will be necessary. A PET camera will be provided in one of the treatment rooms, to check that the distribution of the dose in the target volume complies with that specified in the treatment plan. The Lyon hospital environment will provide additional clinical diagnostics to that provided at the centre.

Table XIII-1 below lists the equipment necessary for three treatment rooms and the associated technical areas.

Description	Equipment
Treatment plan room 1	2 planimetry consoles
Treatment plan room 2	2 planimetry consoles
Computer storage and archive room (images, etc)	Planned in the control system
Pre-positioning room 1	Lasers, mobile support table + trolley
Pre-positioning room 2	Lasers, mobile support table + trolley
Pre-positioning room 3	Lasers, mobile support table + trolley
Clinical MRI room	MRI scanner and accessories
Simulation scanner room	Scanner and accessories
Anesthetics room + associated areas	In accordance with current standards
Treatment room 1	3 mobile X-ray tubes with image intensifiers Optical system ("Optotrack" type) Lasers Robot, Bed, Chair Passive mode irradiation device Quality control equipment
Treatment room 2	3 mobile X-ray tubes with image intensifiers Optical system ("Optotrack" type) Lasers Robot, Bed, Chair Suitable PET camera Quality control equipment
Treatment room 3	3 mobile X-ray tubes with image intensifiers Optical system ("Optotrack" type) Lasers Robot, Bed, Chair Quality control equipment
Irradiation control room 1	2 stations and associated equipment
Irradiation control room 2	2 stations and associated equipment
Irradiation control room 3	2 stations and associated equipment
Immobilization device preparation room	Specialist machines and tools
Workshops and technical areas	Machines tools, etc
Offices	Equipment
Meeting room	Equipment

Table XIII-1: medical equipment

• XIV •

Capital costs, development program, development staff

XIV-1
Capital costs

The estimates given below are presented in a summarized form. They have been prepared in detail (while still remaining in the context of a preliminary design):

- by analyzing the sub-systems which have been studied in other projects (HICAT injector, PIMMS synchrotron),
- by the detailed study of new points (beam lines, control system, computer systems),
- by consulting specialist companies or experts for each constituent part (price of magnetic elements, vacuum elements, RF elements, diagnostics). The building, the soil composition of the reference site and the infrastructure (air conditioning, mains power supply) have been the subject of specific studies with the assistance of specialist consultancies and the Property Department of the CNRS.

A global additional cost for contingencies has been incorporated.

A "development staff" item is included in the estimates. This is the project management team and the specialists required for the design and engineering work, the initiation and monitoring of contracts, acceptance, assembly, tests and finally commissioning of the installation. These staff, as for any accelerator, will be present on site during construction. This item does not include the man power required for building the elements of the accelerator as it is included in the services supplied by the manufacturers.

Description	Capital expenditure excluding tax November 2001 prices scenario without rotating isocentric gantry (M€)	Capital expenditure excluding tax November 2001 prices scenario with rotating isocentric gantry (M€)
Production of ions, linear accelerator and low energy beam lines.	8.83	8.83
Synchrotron	6.45	6.45
Beam distribution and scanning system	4.68	10.21
Control	8.25	9
Building and infrastructures (including project management)	23.2	24.6
Equipment for rooms	8.23	8.23
Cost of development staff	15	15
Contingencies 7%	5.22	5.74
Total cost (M€)	**79.86**	**88.06**

Table XIV-1: capital costs

Note: the "building and infrastructures" line includes a system for protecting important equipment against mains power failures (HQPS subsection XI-2-1 in volume II), for a cost of 0.7 M¤.

XIV-2
Project development

The development is based on a period of 6 years including a detailed design stage of around two years. The graph below presents the total capital expenditure plan, including staff and equipment (figure XIV-1). The scenario shown is that with a rotating isocentric gantry. The main expenditure is as follows :

- the contract relating to the project management of the building will be started in the first year,
- the funding of the building and entire infrastructure will be started in the second year,
- the funding of most of the main equipment (high technology components) will be started in the third year,
- the funding of the control system will be started in the fourth year, together with that of part of the medical equipment,
- the capital expenditure in the fifth year will be devoted to the remainder of the medical equipment,
- the sixth year will be devoted to machine testing ("pre-clinical" period) and validation of the treatment system and to administrative licensing for treatment. This year corresponds to "year 0" of the centre increase to full capacity, during which the first patients will be treated.

The possibility and methods of collaboration with organizations, either French (the CEA or CNRS laboratories for example) or European (CERN, GSI, TERA), must be anticipated in order to take advantage of their considerable experience (synchrotron aspects for CERN and TERA, injector for GSI, for example).

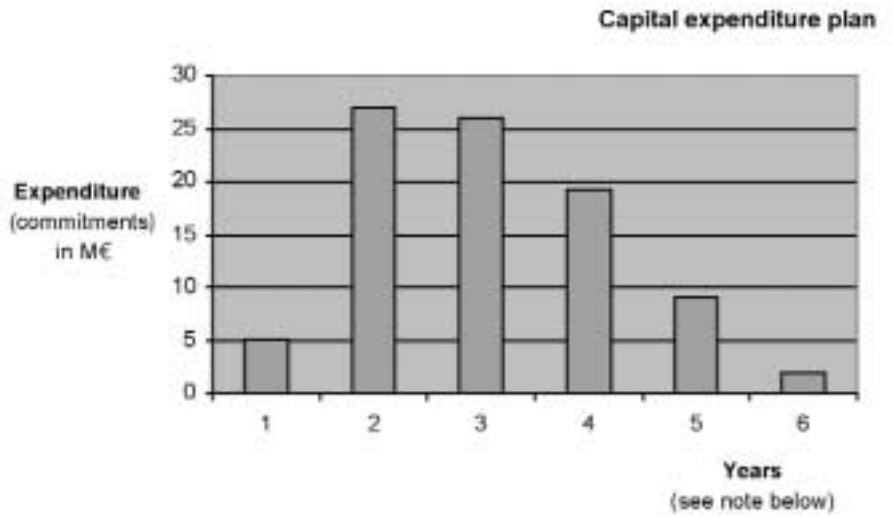


Figure XIV-1: capital expenditure plan, including staff and equipment (including 7% for contingencies) for a scenario with rotating isocentric gantry

Note: year 1 is the year of the decision in principle to go ahead with ETOILE. Year 2 is the year of the final decision. Year 6 is "year 0" of the centre's increase to full capacity, during which the first patients will be treated.

XIV-3
Development staff

The following graph shows the planned numbers of staff managed directly by the project and required for its development (figure XIV-2).

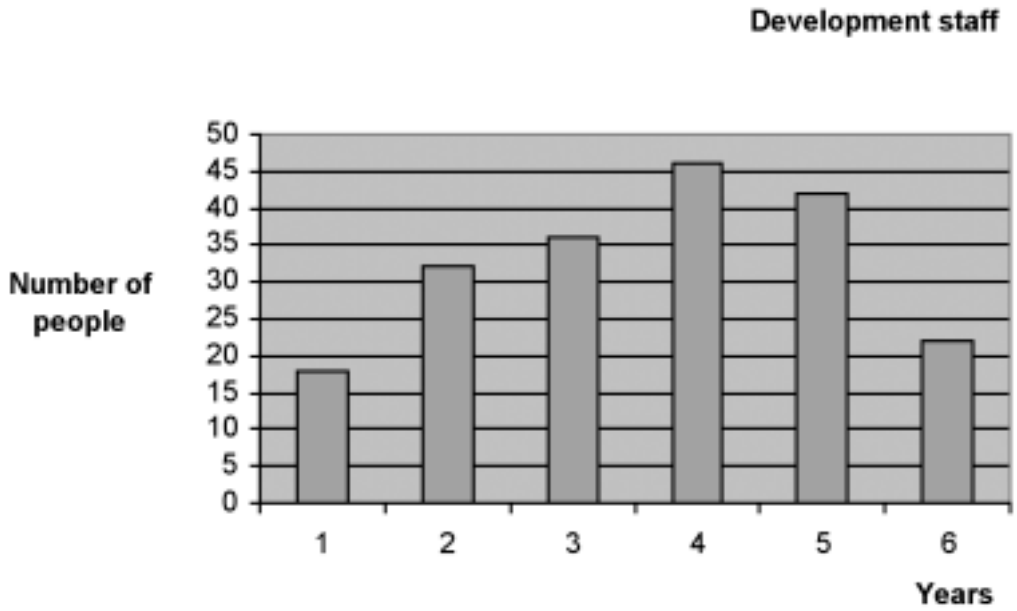


Figure XIV-2: staff involved during the development phase

The "responsibility for development" cannot, in our opinion, be totally assigned to a manufacturer which would have to guarantee the performance of a turn-key installation which it had never built before. The same argument was used in [6].

• XV •

Technical operation

XV-1
Technical staff during operation

With these assumptions, the technical staff required is estimated below. It is important to note that this is the minimum staffing necessary, with no safety margin. Administrative and technical staff are not included.

The experience of GSI indicates that it is necessary to have machine operation expertise available during the treatment period, at the treatment room consoles, as well as the operator (medical staff). It is assumed that during this period, the "main" machine console is on standby and monitors the parameters.

Operation - Morning shift

A technical manager must be present.
A system manager must be present, in view of the high degree of automation of the centre.
Adjustment and testing phase: 2 operators at the main console
Treatment phase: one of the operators will be available for the 3 rooms. The second operator will remain at the main console.

Total 4 people minimum for operation for the first shift.

Operation - Afternoon shift

The scenario will be similar for the afternoon shift, replacing the adjustment phase with the checking phase.

Total 4 people.

Staff not assigned to a shift

In order to provide constant servicing and in particular first level repairs taking less than one hour, the following staff will be distributed over the two shifts :
Radiofrequency, diagnostics, sources: 1 engineer and 1 technician
Vacuum, electromechanics, mechanics: idem
Power electronics, electronics : idem
Night watch: 2 technicians (this is a minimum as the watch period is 10 hours)

Total: 8 people

General total: 7 engineers and 9 technicians, i.e. 16 people minimum.

This is a minimum number which gives an average of 5 to 6 technicians at the centre, for the 5-day 35-hour weeks worked. It does not include either any overlapping of technical teams and time for giving instructions, or holidays. However, it is assumed that the machine will be sufficiently reliable to enable overlapping and include holidays.

XV-2
Costs connected with technical operation

These are annual values, based on 2001 prices, in M¤ excluding tax (excluding staff).

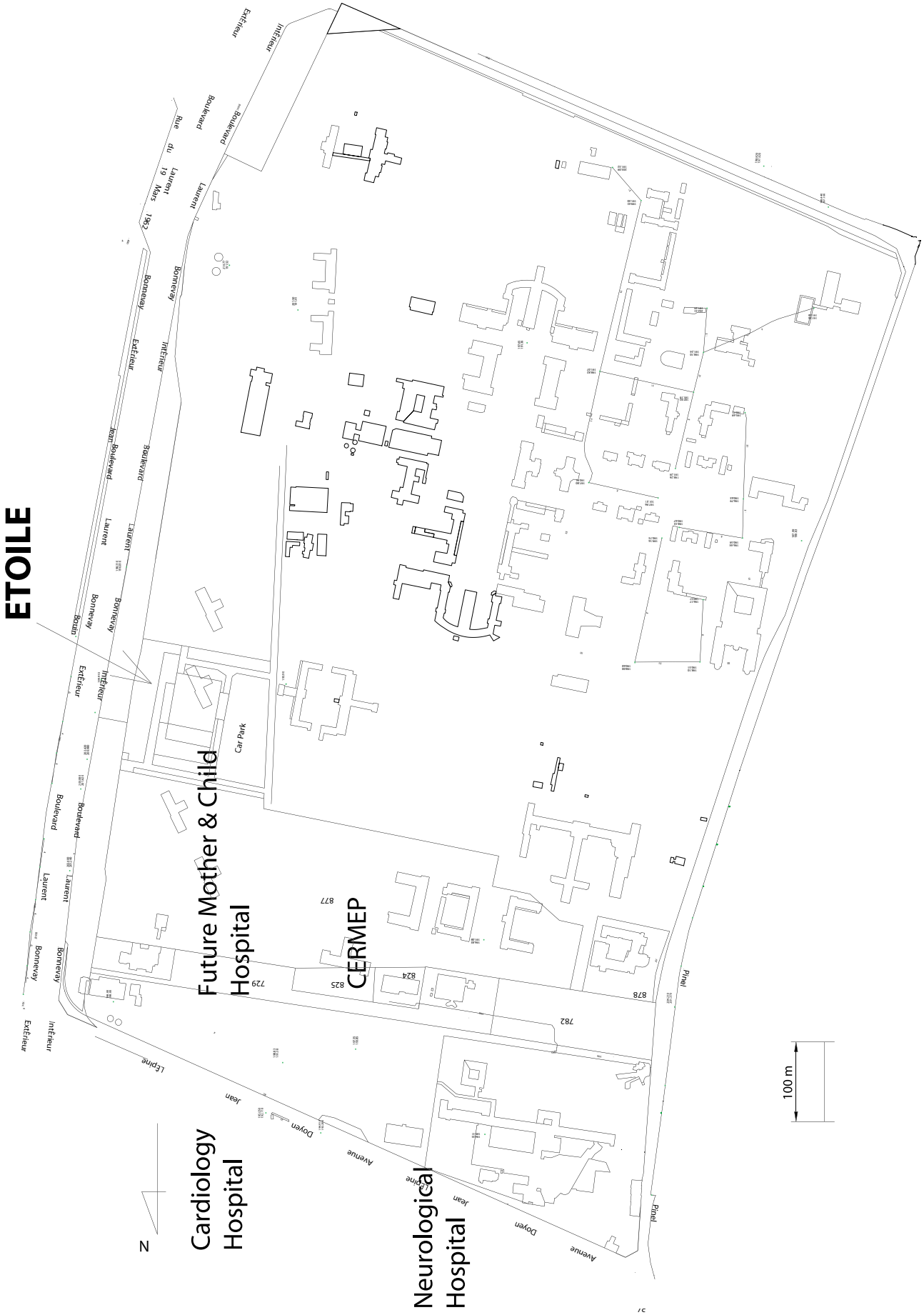
Electricity	0.70
Fluids	0.08
Maintenance of infrastructures	0.23
Maintenance of buildings	0.09
Maintenance of the accelerator	0.83
Accelerator improvements, updates	0.43
Development of medical software and equipment	0.23
Fixed costs (land, insurance, security, etc)	0.22
Total	**2.81 M€**

Table XV-1: costs connected with technical operation (excluding staff)

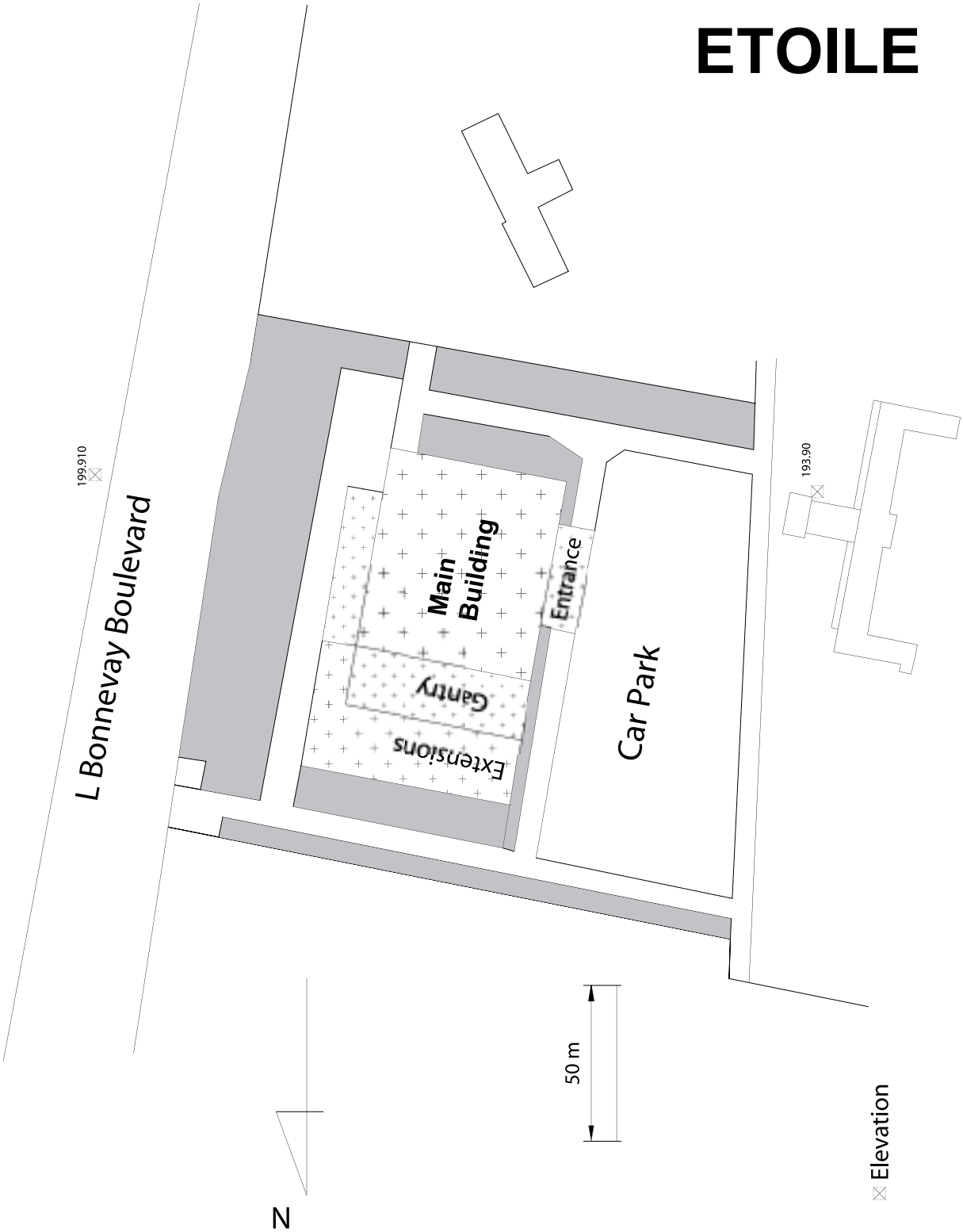
• XVI •

Plans and diagrams

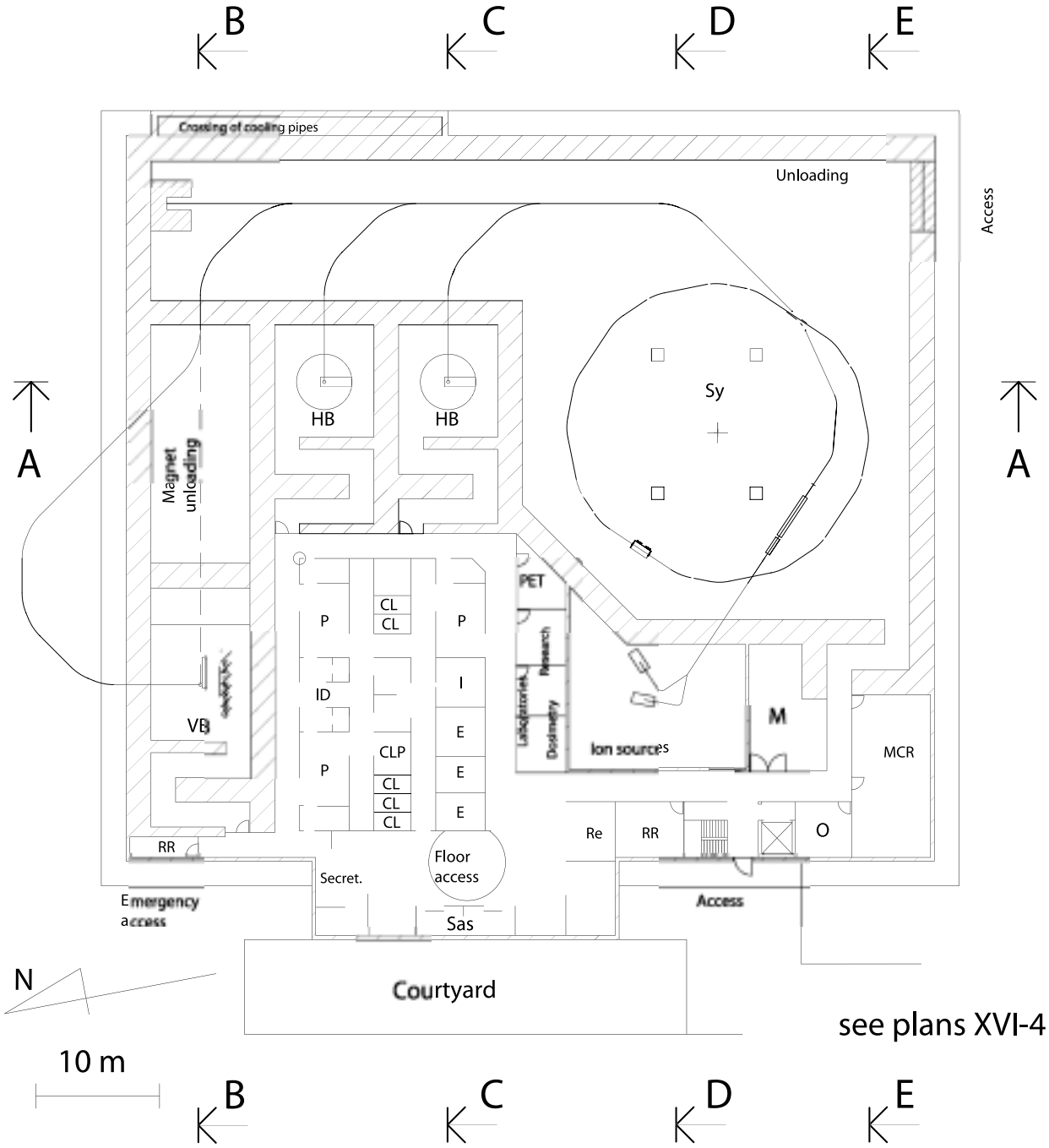
XVI- 1 Vinatier site



XVI- 2 Building layout



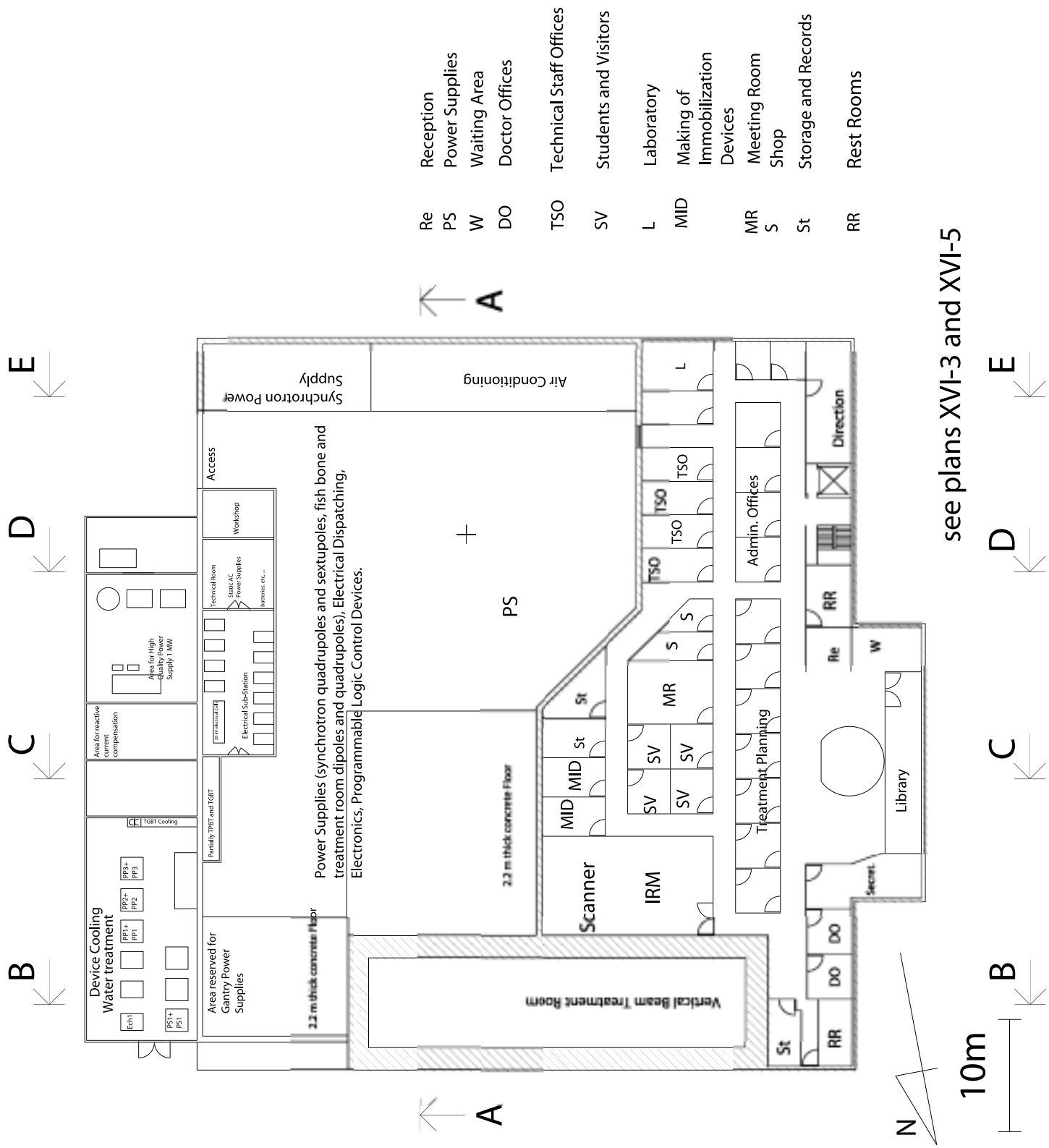
XVI- 3 Building without gantry : treatment floor



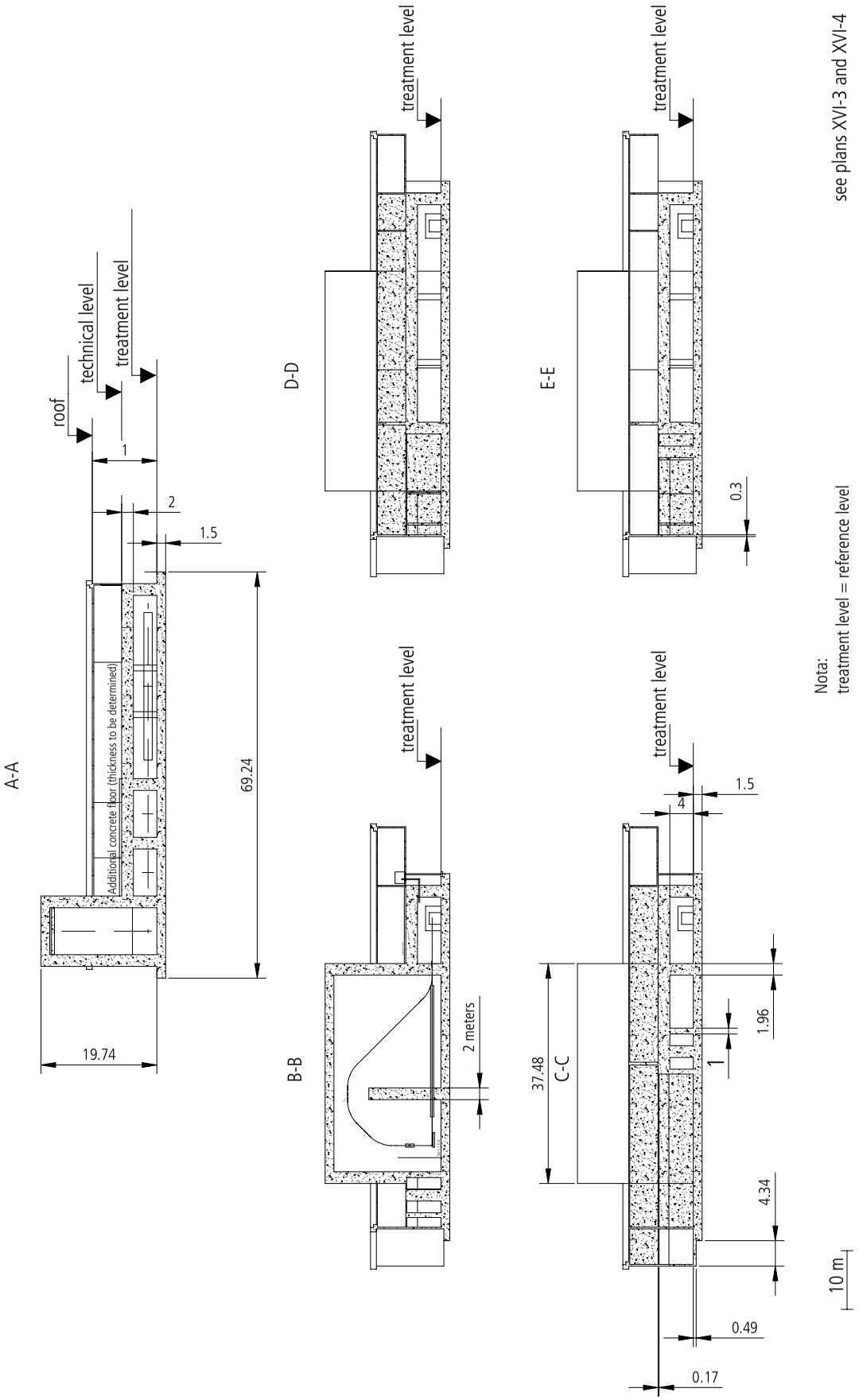
A	Anaesthesia
Re	Reception
W	Waiting Area
C	Control
E	Examination
HB	Horizontal Beam treatment room
VB	Vertical Beam treatment room
I	Infirmary
M	Maintenance
ID	Storage of immobilization devices
O	Operators
P	Pre-positioning
MCR	Main Control Room- Computers
Sy	Synchrotron
RR	Rest Rooms
PET	Positron Emission Tomography
CL	Cloakroom
CLP	Cloakroom for lying patient

see plans XVI-4 and XVI-5

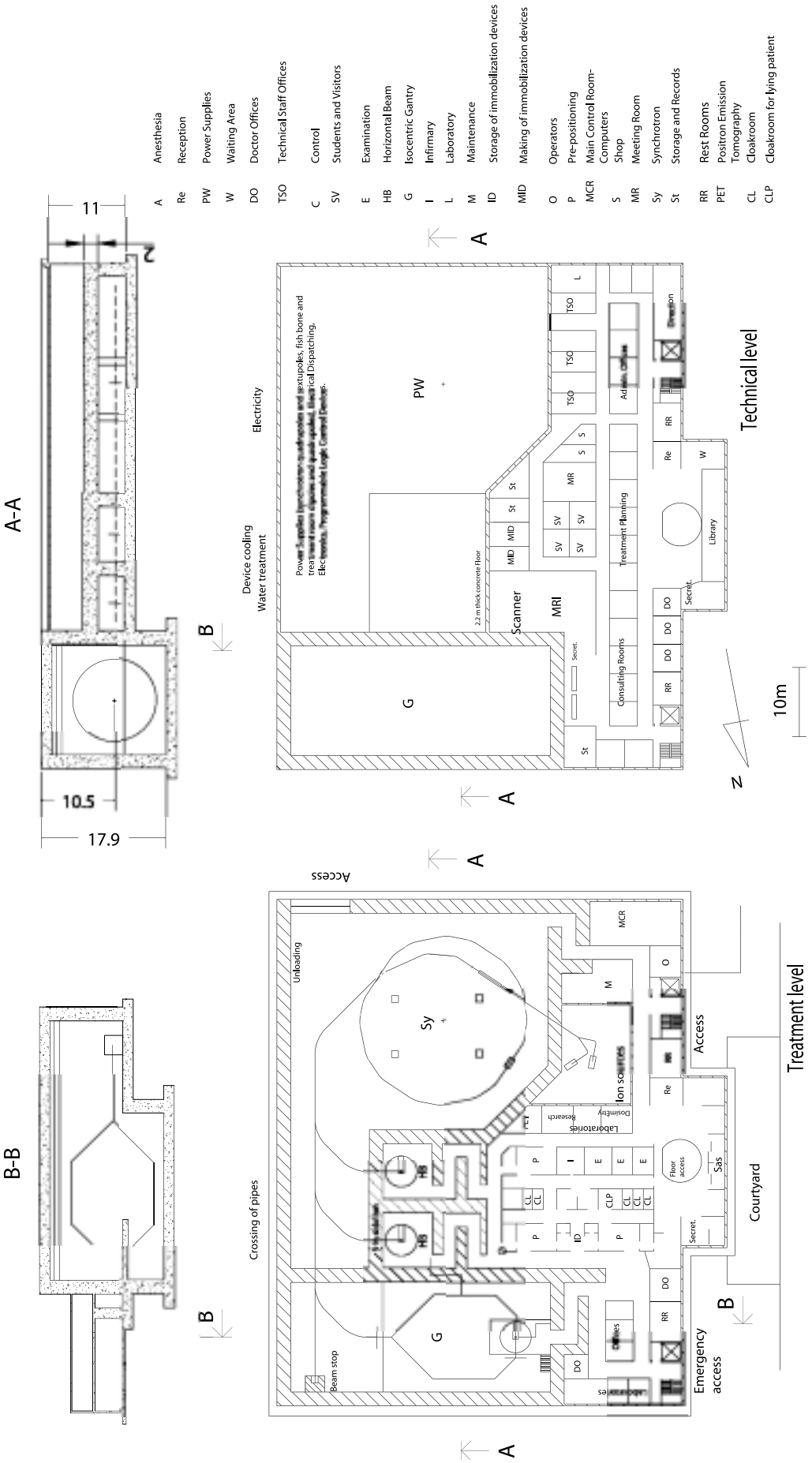
XVI- 4 Building without gantry : technical floor



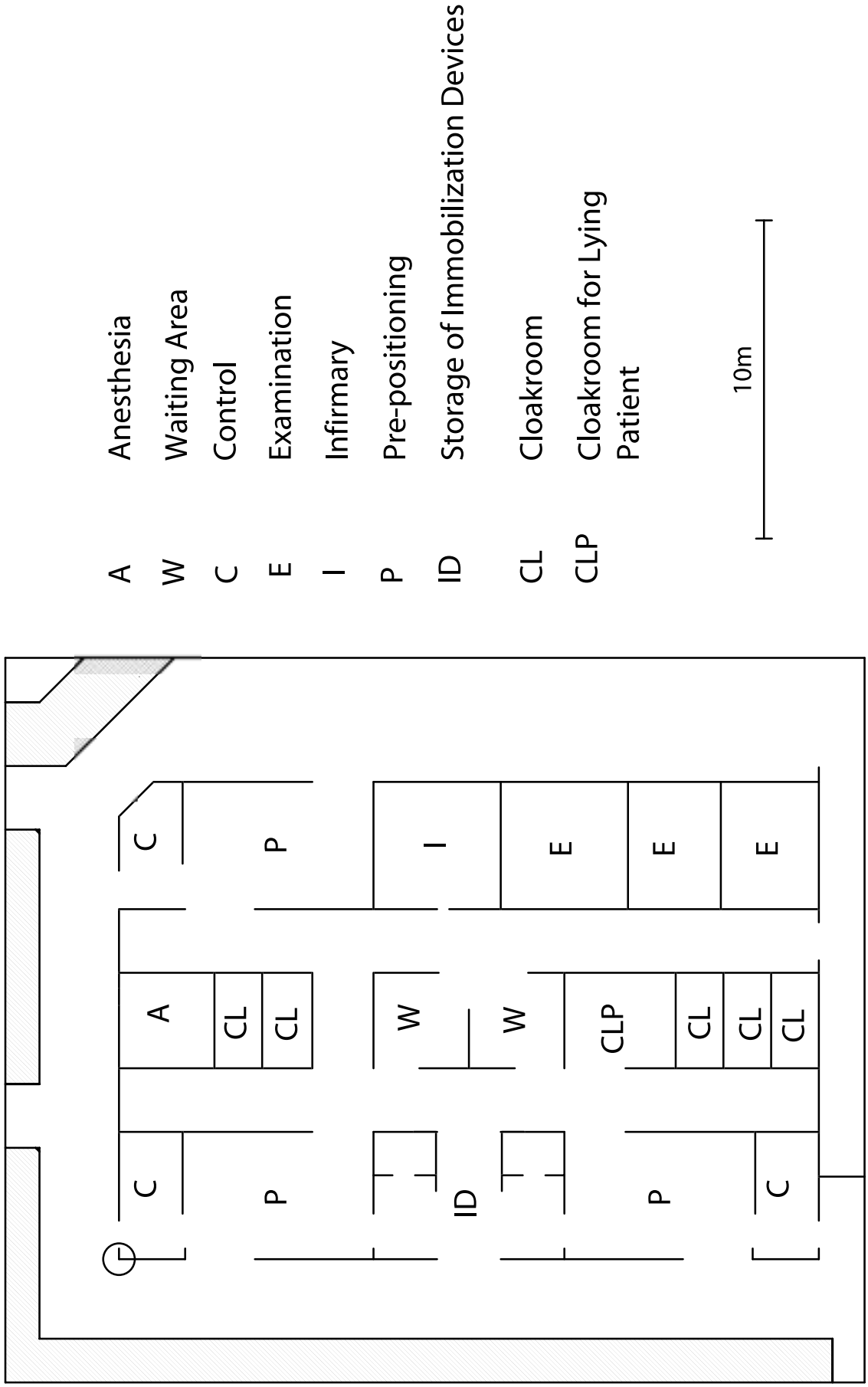
XVI- 5 Building without gantry : sectional drawings



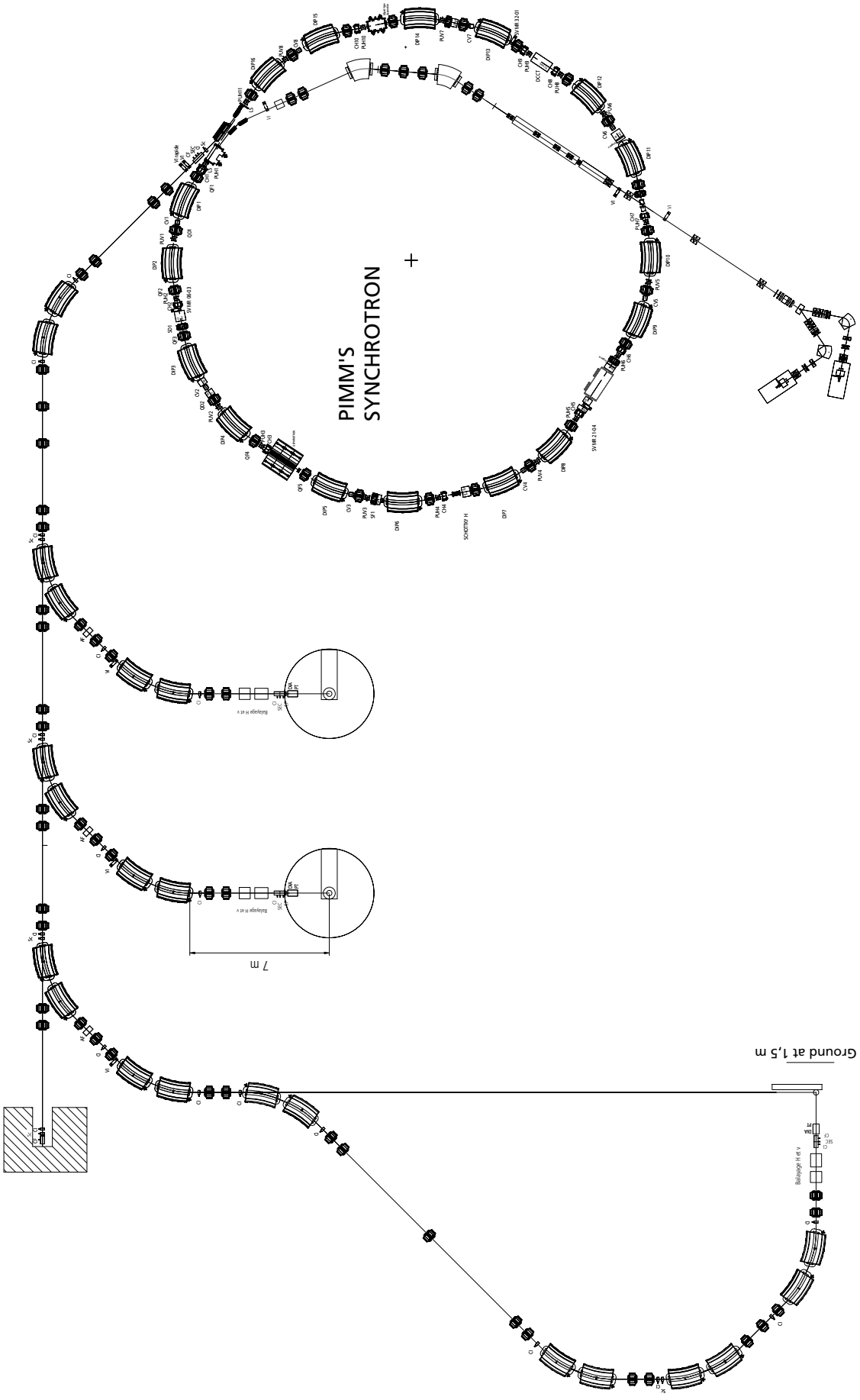
XVI- 6 Building with gantry : plans and sectional drawings



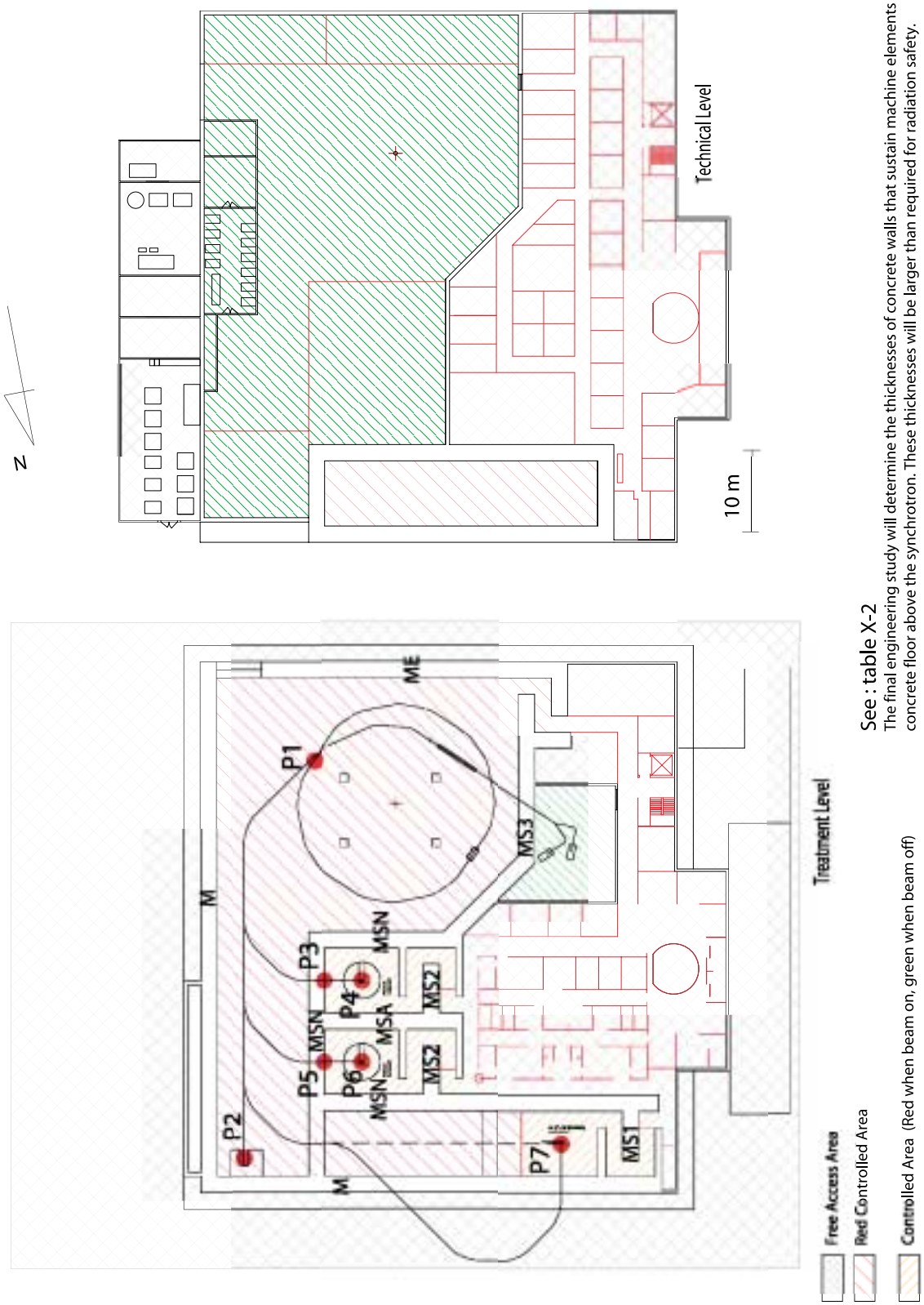
XVI- 7 Patient areas



XVI- 8 Synchrotron and beam lines

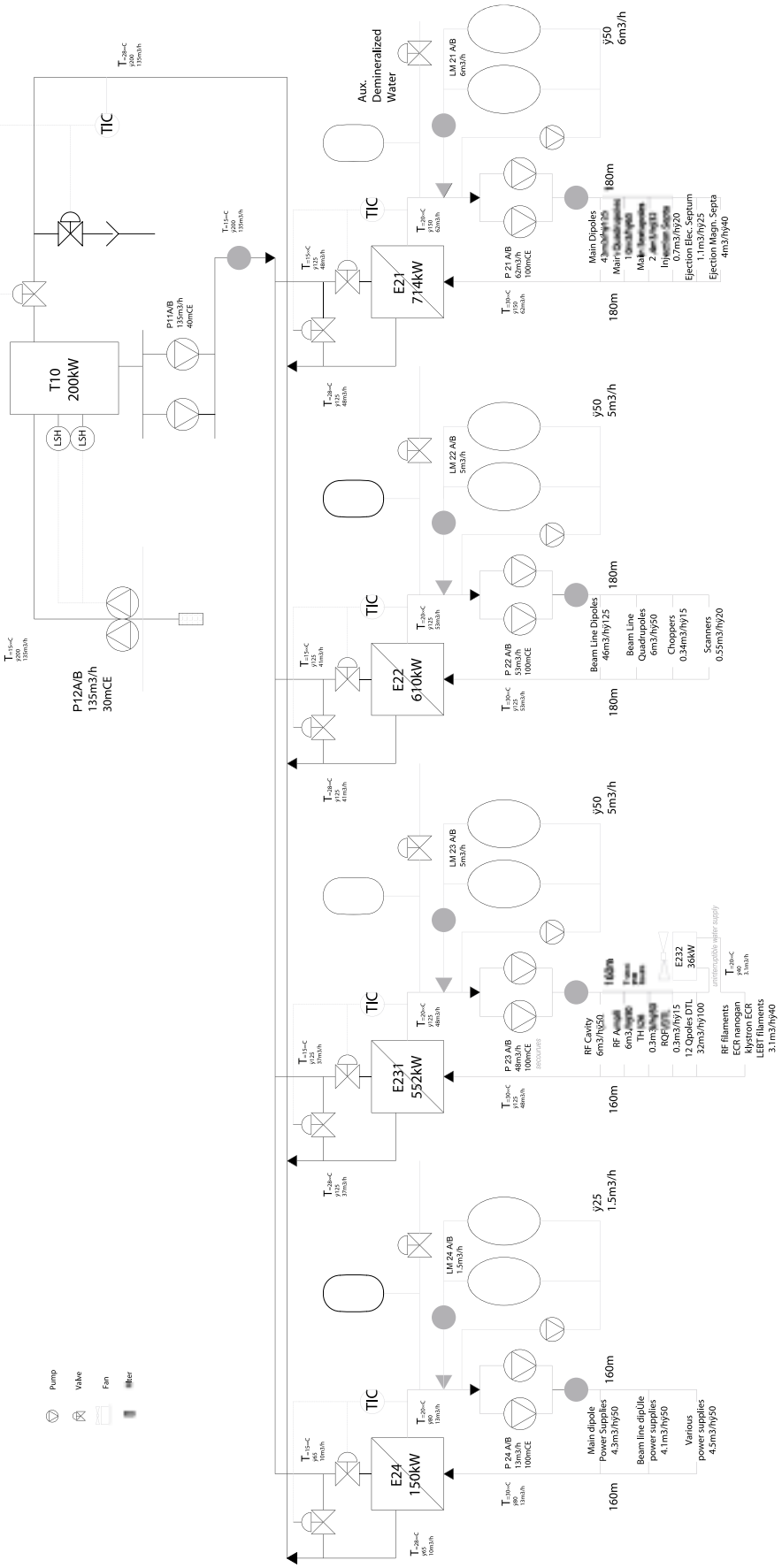


XVI- 9 Controlled zones and beam loss points

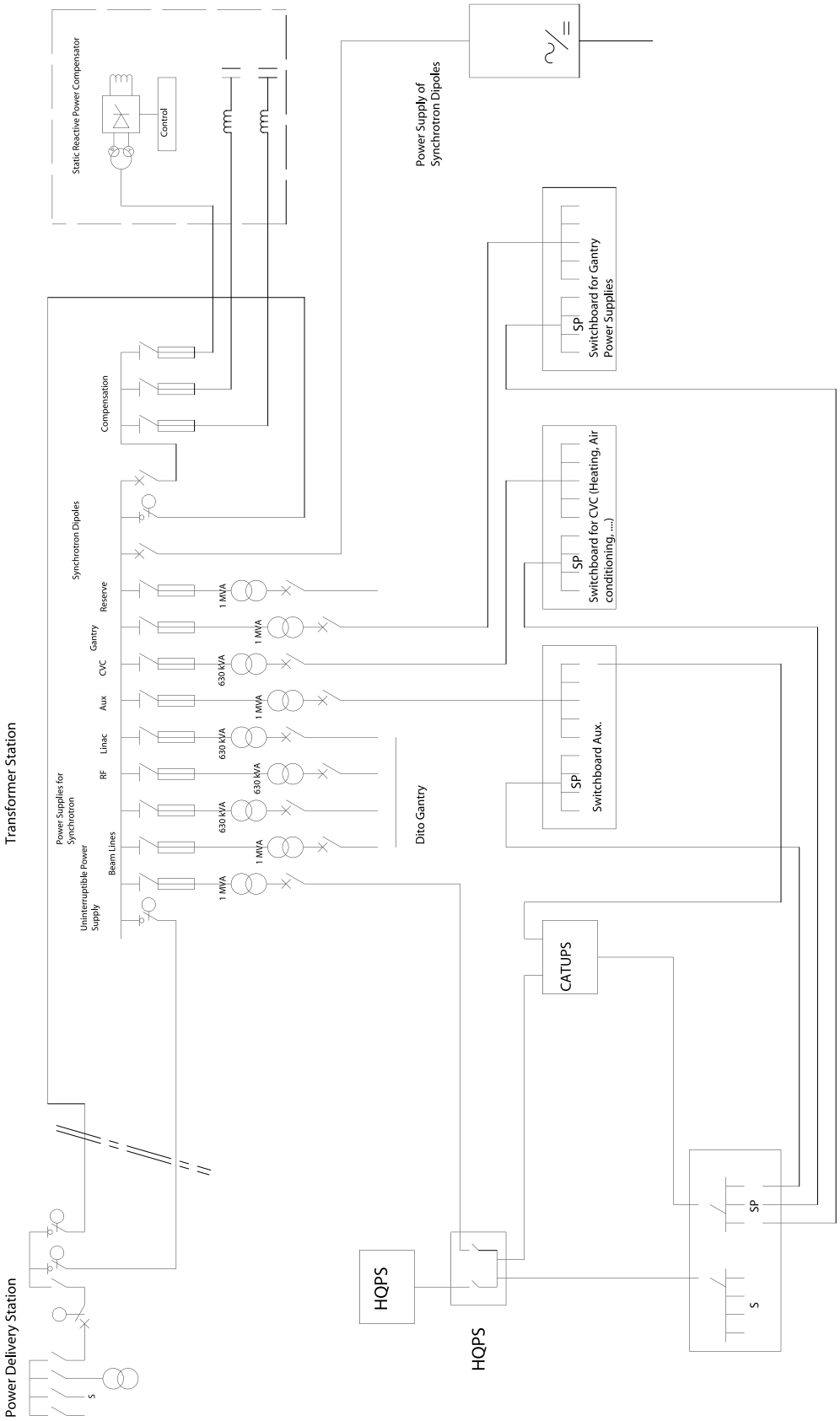


See : table X-2
The final engineering study will determine the thicknesses of concrete walls that sustain machine elements and the concrete floor above the synchrotron. These thicknesses will be larger than required for radiation safety.

XVI- 10 Diagram of the equipment cooling system : solution using ground water



XVI- 11 HV and LV electrical power distribution diagram



• XVII •

Acronyms and abbreviations

APD	*Avant Projet Détaillé* Detailed Preliminary Design
APS	*Avant Projet Simplifié* Simplified Preliminary Design
CCTP	*Cahier des Clauses Techniques Particulières* Specific Technical Specifications
CEA	*Commissariat à l'Energie Atomique* Atomic Energy Agency
CERMEP	Positron Emission Medical Investigation and Research Centre
CERN	*Centre Européen de Recherche Nucléaire European* Organization for Nuclear Research
CNA	Centro Nazionale di Adroterapia Italian hadrontherapy project
CNRS	*Centre National de la Recherche Scientifique* National Scientific Research Centre
CPU	Central Processing Unit
DESY	Deutsche Synchrotron German Synchrotron
DRR	Digitally Reconstructed Radiography
DSM	*Direction des Sciences de la Matière* (CEA) Material Sciences Department
DSP	Digital Signal Processor
DSV	*Direction des Sciences du Vivant* (CEA) Life Sciences Department
DTL	Drift Tube Linac
ECR	Electron Cyclotron Resonance
ENLIGHT	European Network for Light Ions Therapy
EPAC	European Particle Accelerator Conference
EPICS	Experimental Physics Industrial Control System
EPROM	Erasable Programmable Read Only Memory
Gantry	Treatment room with rotating isocentric gantry
GPIB	General Purpose Interface Bus
GSI	Gesellschaft für Schwerionenforschung Society for heavy ion research
HICAT	Heavy Ion Cancer Therapy Facility
HIMAC	Heavy Ion Medical Accelerator of Chiba
IN2P3	National Institute for Nuclear and Particle Physics
IPNL	*Institut de Physique Nucléaire de Lyon* Lyon Nuclear Physics Institute
ISNG	*Institut des Sciences Nucléaires de Grenoble* Grenoble Nuclear Science Institute
LBNL	Lawrence Berkeley National Laboratory
LED	Luminescent Electronic Diode
LINAC	LINear ACcelerator
MRI	Magnetic Resonance Imaging
MWPC	Multi Wire Plate Chamber
NAS	Networked Attached Storage
NIRS	National Institut of Radiologocal Sciences
PC	Personal Computer
PET	Positron Emission Tomography
PIMMS	Proton Ion Medical Machine Study
PPIC	Parallel Plate Ionization Chamber
PPMA	Polymethyl MethAcrylate
RAID	Redundant Arrays of Independent Disks
RFQ	Radio Frequency Quadrupole
SOBP	Spread Out Bragg Peak
TCP-IP	Tranmission Control Protocol-Internet Protocol
TERA	Fondazione per Adroterapia Oncologica Foundation for Oncological Hadrontherapy
TJNAF	Thomas Jefferson National Accelerator Facility
UCBL	Université Claude Bernard Lyon 1
UMA	*Unité de masse atomique* Unit of atomic mass
VLAN	Virtual Local Area Network
VME	Versa Module Europe (data acquisition bus standard)
VXI	VME Extension for Instrumentation

• XVIII •

Figures and tables

XVIII-1
Figures

XVIII-2
Tables

• XIX •

References

[1] D Böhne. *Synchrotrons for cancer therapy.* EPAC 1992 p 217

[2] P Mandrillon et al. *Feasibility studies for the EULIMA light ion medical accelerator.* EPAC 1992 p 179

[3] U Amaldi et al. *A hospital based hadrontherapy complex.* EPAC 1994 p 49

[4] P Mandrillon. *High energy medical accelerators.* EPAC 1990 p 263

[5] P Bryant. *Developments in the design of proton and ion accelerators.* EPAC 1998 p 207

[6] *Proposal for a dedicated ion beam facility for cancer therapy*. Universitätklinik Heidelberg, Deutsches Krebsforschungzentrum Heidelberg, Gesellschaft für Schwerionenforschung Darmstadt (1998)

[7] *Proton-Ion Medical Machine Study.* Part I, CERN/PS 99-010 (DI) March 1999 & Part II, CERN/PS 2000-007 (DR) May 2000

[8] P Sortais et al. Review of scientific instruments 69 (1998) 656

[9] *The injector linac HICAT*. Private communication (GSI)

[10] B Schlitt and U Ratzinger, *Design of a carbon injector for a medical accelerator complex.* Proceedings of EPAC1998, Stockholm, Sweeden (p 2377)

[11] B Schlitt et al. *Design of the 7 MeV/u 217 MHz injector linac for the proposed ion beam facility for cancer therapy at the clinic in Heidelberg.* Proceedings of LINAC2000, Monterey, USA (p. 226)

[12] A Bechtold et al. *Development of an RFQ-Injector for a therapy-synchrotron.* Proceedings of EPAC2000, Vienna, Austria (p. 2500)

[13] W Barth et al. *Commissioning of IH-RFQ and IH-DTL for the GSI high current linac.* Proceedings of LINAC2000, Monterey, USA (p. 229)

[14] W Barth and P Forck. *The new gas stripper and charge state separator of the GSI high current injector*. Proceedings of LINAC2000, Monterey, USA (p. 235)

[15] KD Grob and M Pavlovic Editors. *Proposal for a dedicated ion beam facility for cancer therapy.* GSI, Submitted in September 1998

[16] PY Lanfrey. Projet de hadronthérapie à Lyon. *Optimisation des nouveaux paramètres d'injection en proton* à 7 MeV DAPNIA/SEA-01-27

[17] M Crescenti. *TERA communication for ETOILE.* Février 2002

[18] F Méot, M Bajard. Design of ETOILE Medium Energy Beam Line, internal report DAPNIA/SACM-02-20, CEA Saclay 2002

[19] M Crescenti. *Insertion of a debuncher cavity*. GSI arbeitnotiz KLB22110.SI 22/11/2000

[20] H Bruck, JL Laclare, G Leleux. *Extraction à l'aide d'une accélération bêtatron.* Report by DSS.SOC.RS.73.13, LNS, CEA Saclay 1973

[21] M Crescenti. *Progress in the study of PIMMS injection line for protons and carbon ions.* PIMMS note, June 1998

[22] M Crescenti. *Status of a 7 MeV/amu injection chain for the CNA*. TERA 2001/10, ACC35

[23] F Méot, A Tkatchenko. *Projet de hadronthérapie à Lyon. Revue de l'injection dans PIMMS et variantes (protons de 7 MeV injection extérieure)*. Report by CEA/DSM/DAPNIA/SEA-01-09 and CNRS/IN2P3/IPNO-01-06

[24] JL Laclare, JM Lefebvre, PA Chamouard, A Ropert et al. *MIMAS*. Nouvelles de Saturne. Information bulletin no. 9B. April 1984

[25] A Dolinskii, H Eickhoff, B Franczak. *The synchrotron of the dedicated ion beam facility for cancer therapy, proposed for the clinic in Heidelberg*. Proc. EPAC 2000, p 2509

[26] B Launé, F Méot, A Tkatchenko. *Projet d'hadronthérapie à Lyon. Lignes de faisceau,* internal reportDAPNIA/SEA-01-10 (CEA) and IPNO-01-07 (CNRS) July 2001

[27] R Ferrand (Centre de Protonthérapie d'Orsay), private communication

[28] P Spiller et al. *Gantry studies for the proposed heavy ion cancer therapy facility in Heidelberg*. Proc EPAC 2000 Vienna p 2551

[29] M Thivent (CERN) private communication

[30] O Delferrière, D De Menezes. *Définition du dipôle des lines de faisceaux pour le projet d'accélérateur pour la hadrontherapie*. CEA/DSM/SEA

[31] JL Jannin and A Sinanna. *Les alimentations de puissance pour un accélérateur médical*. Projet Hadronthérapie Rhône-Alpes. Report by CEA DAPNIA/SEA/IPHI 2001-71

[32] P Ausset, T Aniel, C Fougeron, JM Lagniel. *Large frequency swing* R.F. cavities for M.I.M.A.S. E.P.A.C.1988

[33] C Fougeron, P Ausset, J Peyromaure. *Towards the construction of an ultra short cavity for heavy ions.* E.P.A.C. 1990

[34] P Ausset, G Charruau, D De Menezes, FJ Etzkorn, C Fougeron, H Meuth, S Papureanu, A Schnase. *A high power multiple harmonic acceleration system for heavy ion synchrotrons.* P.A.C. 1995

[35] M Crescenti, G Primadei, A Susini. *A new compact large frequency swing R.F. system for hadron acceleration: test results.* CERN/ PS 97 060 (DI)

[36] L Degueurce, P Ausset. *Beam diagnostics for heavy and polarized ions in the range of 10 keV/amu to 1 GeV/amu.* E.P.A.C. 1988

[37] M Bajard et al. *Projet de centre de traitement des tumeurs radiorésistantes par faisceau d'ions légers (hadronthérapie). Aspects liés à la sûreté de l'installation et à la qualité du traitement.* HAD/PRO/SUR/01.001 Université Claude Bernard Lyon 2001

[38] Th Haberer et al. *Magnetic scanning system for heavy ion therapy.* NIM A330 (1993) p 296

[39] J Balosso, P Pommier, S Rossi, D Sappey-Marinier. *Compte-rendu de visite au Japon.* September 1999

[40] F Méot and T Aniel. *Principles of the non-linear tuning of beam expanders.* NIM A 379 (1996) 196-205

[41] WP Jones and GPA Berg. *Design of a beam transport system for a proton radiation therapy facility.* IUCF, Proc. 1999 PAC Conf., N.Y. (1999) 2519-2521

[42] CISCO Systems Inc, www.cisco.com

[43] CheckPoint Software Technology Ltd, www.checkpoint.com

[44] Group3 Technology Ltd, www.group3technology.ccom

[45] EPICS, mesa53.lanl.gov/lansce8/EPICS/epics.htmICALEPCS'95, Chicago

[46] Wind River Systems, www.windriver.com

[47] U Krause et al. Adaptation of a synchrotron control system for heavy ion tumor therapy. ICA-LEPCS'95, Chicago

[48] Pentek, **www.pentek.com**

[49] Research Systems, **www.researchSystems.com**

[50] Oracle Corporation, **www.oracle.com**

[51] Network Appliance, **www.netapp.com**

[52] ATL, **www.atlp.com**

[53] VERITAS, **www.veritas.com**

[54] H Eickhoff, Th Haberer. *Private communication*

[55] Brusasco et al. *A dosymetry system for fast measurement of 3D depth dose profile in charged particle tumor therapy with scanning techniques.* NIMB 168 2000 578-592

[56] R Antoni, L Bourgois. *Calculs de radioprotection autour d'un accélérateur pour la hadronthérapie.* DEN/SAC/DSP/SPR/SRI-T/01-832

[57] JF Bouteille (ESRF). *Private communication*

[58] Consultation for UPS

[59] M Ducourneau (CEGELEC) en collaboration avec EDF. *Etude de la distribution électrique du projet ETOILE.* Novembre 2001

[60] A Bengio (Ouroumoff Ingénierie). *Projet ETOILE : circuits de réfrigération et de climatisation.* Novembre 2001

[61] *Plan d'occupation des sols. Communauté Urbaine de Lyon,* secteur EST-Bron

[62] *Données climatologiques concernant la zone Lyon-Bron.* Septembre 2001

Notes