Hadrontherapy - macrobenefit in cancer therapy?

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Abstract. Hadrontherapy is one of the most promising radiotherapeutical innovations that deal with accelerated heavy charged particles, mainly proton and carbon ions. Their salient features include an original dose-distribution, based on the Bragg curve, and in some of them an increased RBE at the range-end. Approximately 100 000 patients have been treated so far in approximately 40 centers worldwide. Outstanding outcomes have been substantiated in rare neoplasms using protons, such as ocular melanomas, skull base sarcomas, and pediatric malignancies, while only promising evidences have emerged using carbons. Assessing their place in more common tumor-sites, such as lung, pancreas, prostate, esophagus remains to be determined, and justifies the expansion of future particle therapy programs.

1. Background

Radiation therapy (RT) along with surgery represents the mainstay of local treatment of cancer. In France, approx 180 000 patients are treated annually using RT, and 600 000 in Europe. On the other hand, it is established that an efficient local treatment can, to some extent, prevent a metastatic evolution of the disease. In this context, RT has enjoyed considerable improvements since the early 90s that make it safer and more efficient. Most of these innovations have become possible because of dramatic developments of imaging (especially 3D imaging) that considerably benefit treatment preparation and verification, and computer technologies that are part of all modern equipment (including linear accelerators, gantries, robotised couches...). Public attention has been recently attracted by the capabilities for producing a modulated intensity of the beam (IMXRT), a sophisticated delivery mode that allows strict conformation of multiple beams, “shaped” dynamically in modulated fluence to the target using a “reverse” treatment planning (algorithms take into account specified dose and volume constraints for tumor, and normal organs to generate beams’ arrangement and intensity). Helical tomotherapy and cyberknife, the most advanced technologies in this field, are also derived from IMXRT [1]. Nonetheless, all these technologies are based on a single type of radiation: photons (i.e. X-Rays) that have been in use for over a century! Limitations of photon beams are correlated with their physical properties in matter characterised by a progressive attenuation, a substantial “exit” dose at the end of path, and finally unnecessary exposure of anatomical structures beyond the target. Furthermore, part of the tumors are known to be poorly sensitive to photons, (due to cell intrinsic radioresistance, fast multiplication, hypo-oxygenation…), while most normal tissues express immediate and/or delayed radio-induced toxicity, above a specific dose-level. These limitations have stimulated the interest for new approaches that improve tumor sensitivity (through combinations with cytotoxic drugs, biological agents…), or normal tissues tolerance (by radioprotectant agents,

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2. A brief history of the charged particle therapy world

In 1946, R Wilson, a physicist at the Harvard Cyclotron (MA, USA) wrote a seminal paper in which he pointed out that a high energy proton beam could be effective for cancer therapy since it produced a greater ionisation density at the end of its path. This physical property has actually been described earlier on (1904) by WH Bragg, and is since known as the Bragg curve or simply the “Bragg peak” (BP). This paper triggered early biological and later clinical experiments, first conducted by a few neurosurgical teams. Remarkably, these experiments represented a limited part of large basic physics programs. In the seventies it became evident that most conventional cyclotrons and synchrocyclotrons (SC) were obsolete for nuclear physics research. But in their energy-range (approx 150 MeV: 16 cm penetration in water) particles could reach many deep-seated tumor sites. Consequently, ophthalmological and neuro-oncological clinical programs quickly developed under the supervision of physicians and physicists initially at Massachusetts General Hospital (MA, USA). Similar developments followed in foreign countries, including France where in 1991, the nuclear physicists “passed the baton” to radiation oncologists at the 201 MeV Orsay SC. In parallel, more limited programs dealing with light ions (neon, carbon, silicium...) were conducted at BEVALAC (CA, USA) until the unfortunate shut-down of all physics and medical applications in 1993. We will also mention the negative pions which were piloted in two centers (TRIUMPH, Vancouver, Canada, and PSI, Villigen, Switzerland). Eventually, the message was passed that carbon ions could represent the optimal particle in terms of ballistical and biological advantages. This stimulated intensive investigations dealing with carbon both in Japan (HIMAC, Chiba), and Germany (GSI, Darmstadt). In the 2000s sustained interest in protontherapy applied to new indications led to the development of modern turn-key facilities, developed by a few industrial companies located in Japan, Belgium, and Germany. Although synchrotron technology gained wide acceptance, a renowned interest for innovative compact high energy cyclotrons emerged recently. Similarly, synchrotron-based development of carbon centers was achieved on a more modest scale in a few places (located in Japan and Germany, so far), although the cyclotron technology has its own supporters. It is also remarkable that recent modes of dose-delivery have been mimicking advanced photon innovations (i.e. isocentric gantries, multi leaf-collimators, spot-scanning applied to intensity modulation...) so that hadron-patients can benefit from the highest levels of sophistication.

3. Clinical benefit of hadrontherapy

Following pioneering work initiated in the 60s in the US, two radiation types have been tested since the early 90s: protons and “light” ions, mainly carbon ions. As off December 2011, 95 000 patients (most with cancers) had benefited from hadrontherapy in 37 centers worldwide, including 31 proton, 4 carbon, and 2 mixed proton and carbon centers[3].

- **Protons** are well adapted to high precision irradiation, due to their Bragg curve dose distribution: the selective absorption of the dose at tumor depth is followed by a sharp fall-off. The lateral “penumbra” is reduced as well compared with most photon dose profiles [4]. All these properties improve sparing of normal tissues located downstream or lateral to the beam (even away by few millimetres only), and allow dose-escalation to the target more safely if improved tumor cell-killing is also contemplated [5]. To some extent, this type of radiation is the best that complies with the ALARA (As Low As Reasonably Achievable) principle that has been recommended for the general population exposed to radiation hazards, esp. in terms of radio-associated carcinogenesis.
Clinical studies have mainly concerned tumors poorly sensitive to radiations, located close to critical sensitive organs, and conducted in approximately 85,000 patients. They are summarized in Table 1. Ocular melanomas represent such a paradigm due to their well-known resistance to X-Rays and vicinity of critical anatomic structures (macula, optic disk...). On approximately 10,000 patients studied, a local control in excess of 95% and a survival rate of 80% have been reported, along with good cosmetic and visual preservation [6]. Slow-growing primary malignancies of skull base and spine (esp. chordomas and chondrosarcomas), although rare conditions, represent a true therapeutic challenge due to their radioresistance, incomplete surgical resectability, and frequent encasement in vital structures (brain stem, spinal cord...). Local control using protons combined with partial resection, has significantly improved the outcome and almost doubled it in poor prognostic subgroups (from approx. 35 to 70%) [7,8]. Pediatric tumors, another rare morbid condition, are also particularly challenging due to the exquisite sensitivity to ionizing radiation of growing normal organs, and documented cosmetic, functional, and sometimes lethal, side-effects observed years or decades following RT. Although chemotherapy still retains the major role in the therapeutic armamentarium, proton therapy (PT) seems optimal, when RT is still indicated [9]. Recently, more common tumor-types such as early lung, or prostate carcinomas have been widely tested, esp. in the US and Japan [10-13]. Encouraging results have been reported, including positive randomized trials supporting the benefit of and good tolerance to high dose PT [14]. An interesting finding was also the improved tolerance to concomitant chemo-radiation combinations, an efficient but highly toxic approach, commonly administered in oncology [14]. Pre-clinical dosimetrical investigations are also paving new avenues to emerging indications, so that the estimated number of patients suitable for PT (sorted out recently by a foreign group) could approach 10 to 15% of all RT patients [15]. This would correspond to 20,000 yearly in France, including 3,500 in the Western and Northern part of the country. This number would by far exceed the current capacities of the two existing French treatment centers (30 or so, worldwide).

Table 1: Relevant clinical series on proton therapy. Abbreviations: dpf: dose per fraction; CGE: Cobalt-Gy equivalent; LC: local control; OS: overall survival.

| Author, date [ref] | Tumor type, #cases | Dose/ dpf (CGE) | Tumor control | Toxicity     |
|--------------------|-------------------|----------------|---------------|--------------|
| Dendale, 2006 [6]  | Ocular melanoma   | 60/15          | LC:96%        | Enucleation: 7% |
|                    | 1406              |                | OS:79%        |              |
| Munzenrider, 1999 [7] | Skull base sarcomas | 67/1.8       | LC:73-98%     | Severe: 3% |
|                    | 519               |                | OS: 80-91%    |              |
| Habrand, 2009 [9]  | Pediatrics        | 50-70/1.8      | LC: 81%       |              |
|                    | 108               |                | OS: 88%       |              |
| Zietman, 2005 [10] | Early prostate    | 70-79/         | LC: 61-80%    | Severe : 1-2% |
|                    | 393               |                | OS: 96-97%    |              |
| Bush, 2004 [11]    | Lung              | 51/5           | LC:74%        |              |
|                    | 68                |                | OS: 44%       |              |
| Sugahara, 2005 [12] | Esophagus        | 76-82/         | LC: 57%       |              |
|                    | 46                |                | OS: 34%       |              |
| Chiba, 2005 [13]   | Liver             | 72/4.5         | LC: 87%       | Severe: 3%   |
|                    | 162               |                | OS: 23%       |              |
- **Light ions:** as mentioned above, initial biological and clinical experiments conducted in North America, led to the choice of carbon ions (\(^{12}\text{C}\)) as the optimal ion species in this field. Further experiments switched to different geographical places (Germany and Japan), including a recent German high tech center (HIT, Heidelberg), and five additional ones in Japan. These high LET particles share, with protons, a high ballistical selectivity, associated with the BP, and indicate additional remarkable biological properties, correlated with increased energy-deposition and nuclear interactions at end of range. Quantitatively, these correspond to an increased Relative Biological Efficiency (RBE) from approx. 1.1 in the entrance channel (where normal tissues are interposed), up to 3 and more in the spread-out BP (where tumor and BP superimpose).

Clinical experience so far, dealing with carbon ions, has been reported for approximately 9,000 patients worldwide, and 1,500 using other ion species (mainly helium and pions) in initial experiments. Carbon ions have been chiefly delivered with peculiar fractionation regimes of the dose, i.e. hypofractionated. Clinical indications are summarized on table 2. They concern mainly radio-resistant advanced malignancies, located close to critical structures. If the benefit over PT remains unclear in its main indications, additional interesting data have been collected in highly radio-resistant tumor-processes, such as mucosal melanomas, bony and soft tissue sarcomas, salivary gland carcinomas, digestive tract primaries...[16-22]. Noteworthily appears the impact on pancreatic carcinoma, an almost uniformly lethal condition. A recent update of the Japanese experience, showed a 5 year survival approaching 100% in selected sub-groups [19]. Re-irradiation of a locally recurrent tumor, following previous irradiation, is another challenging situation (due to poor tolerance of tissues irradiated twice, and poor sensitivity related with hypoxia) in which carbon ions have been tested with promising results. A proton course followed by a carbon boost has also been suggested in most radioresistant processes located in critical anatomical areas. Randomised trials comparing carbon ions

| Author, date [ref] | Tumor-type, #cases | Dose/dpf | Tumor control | Toxicity |
|--------------------|--------------------|----------|---------------|----------|
| Kamada, 2002 [16]  | Advanced bone+soft part sarcomas 64 | 53-74/3.3-4.5 | LC: 88% OS: 46% | Severe: 9% |
| Schulz-Ertner, 2005 [17] | Advanced salivary 29 | 72/3 | LC: 77% OS: 76% | Severe: 3% |
| Combs, 2010 [18]  | Aggressive meningiomas 10 | 68/3 | LC: 86% OS: 75% | None |
| Shinoto, 2011 [19] | Post op pancreas 26 | 30-37/4-4.5 | LC: 100% OS: 53% | Severe: 8% |
| Ishikawa, 2006 [20] | Advanced prostate 142 | 66/3.3 | LC: 99% OS: 88% | No severe |
| Yamada, 2009 [21]  | Recurrent rectal 112 | 67-74/1 | LC: 97% OS: 40% | No severe |
| Ohno, 2011 [22]    | Advanced uterine cervix 22 | 64-72/3-9 | LC: 68% OS: 50% | No severe if bowel<60 Gy |
| Ohno, 2011 [22]    | Advanced uterine corpus 45 | 62-71/3-9 | LC: 68% OS: 50% | No severe if bowel<60 Gy |
against reference photon arms are also underway [23-25]. Two ion-projects have been elaborated in France (ETOILE in Lyon, and ARCHADE in Caen) by multidisciplinary teams of physicists, physicians, and engineers in order to design and build-up comprehensive hadron programs “from bench to bedside”.

4. Socioeconomic impact
Socioeconomic issues are a primary concern in the context of limited health resources in general and potential cheaper therapeutic strategies in the specific area of cancer. Clearly, hadron program investments are five to ten times higher than their photon counterparts’, even those dealing with most advanced technologies. But it was shown that a proton project amortization could be safely achieved if patient accrual were sufficient, by approximately doubling the cost per session of photons [26]. As treatment cost is conditioned at least in part by the total number of sessions, light ions provide additional cost-savings by reducing it: current protocols dealing with carbon in Japan and Germany administer generally the dose in 1 to 3 daily sessions per week (vs 5 for protons and photons). The total number of fractions, usually 30 and more in “conventional” fractionation, is also dramatically reduced in most studies, especially in the Japanese approach (to a total of 4 to 16). In the long run, several aspects also speak in favor of particles and make them attractive: costs of salvage programs and patients’ rehabilitation can be minimized; also prolonged employment together with a good quality of life is expected [27]. Detailed evaluations have been implemented in this field.

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