PARTICLE BEAM RADIOTHERAPY FOR HEAD AND NECK TUMORS: RADIOBIOLOGICAL BASIS AND CLINICAL EXPERIENCE

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Abstract: Background. Head and neck tumors are often located near critical organs, making it impossible to deliver a dose of conventional radiotherapy high enough to eradicate the disease. Our aim was to review the potential benefits and available clinical experience of particle beam therapy (hadrontherapy) in the treatment of these tumors.

Methods. A review of the literature was carried out through a MEDLINE search (publications between 1980 and 2005).

Results. A review of the available clinical data shows that particle beam therapy can offer several radiobiological and physical advantages over conventional photon radiotherapy: improved dose distribution permits dose escalation within the target and optimal sparing of normal tissue. Preclinical and clinical studies suggest that there may be benefits to using hadrontherapy for tumors characterized by poor radiosensitivity and critical location. At present, the most used hadrons are protons and, as yet on an experimental basis, carbon ions. It is now well accepted that there are certain indications for using proton therapy for skull base tumors (chordoma and chondrosarcoma), paranasal sinus carcinomas, selected nasopharyngeal tumors, and neutron/ion therapy for salivary gland carcinomas (in particular, adenoid cystic tumors). Its viability in other cases, such as locally advanced squamous cell carcinoma, melanoma, soft tissue sarcoma, and bone sarcoma, is still under investigation.

Conclusions. Hadrontherapy can be beneficial in the treatment of tumors characterized by poor radiosensitivity and critical location. Further clinical and radiobiological studies are warranted for improved selection of patient population.

Keywords: radiotherapy; hadrontherapy; ions; protons; neutrons; head and neck tumors; particle beam

Radiation therapy, alone or combined with surgery or chemotherapy, can produce lasting locoregional disease control in a high percentage of patients with head and neck cancer. The noninvasive nature of external beam radiotherapy can have advantages over surgery (especially in the case of tumor unresectability or an organ preservation approach), interstitial brachytherapy, and chemotherapy.

Radiotherapy is usually delivered using high-energy X-rays produced by linear accelerators. This is uncharged electromagnetic radiation (photons), with physical properties similar to radio waves or visible light, except that such radiation (“packets” of energy) is energetic enough to ionize molecules in the tissue that they penetrate.
probability of treatment success depends on a number of factors, including tumor stage, radiosensitivity, and radiotherapy-related variables such as dose and treatment precision. Theoretically, it would be possible to cure most patients with head and neck cancer by administering a high dose of radiation. However, in many clinical situations, the dose is limited by the presence of adjacent radiosensitive normal tissues.

The limitations of X-ray radiotherapy can be substantially overcome by using hadrons. Hadrons are subatomic particles subject to a strong nuclear force and they can be employed in a therapy called hadrontherapy or particle beam radiotherapy. Originally, the word “hadrontherapy” was coined to indicate all forms of treatment that use beams of hadrons (ie, beams of particles made up of quarks such as neutrons, protons, and ions). The first experience of hadrontherapy included treatment with neutrons in 1930, with protons in 1954, with helium ions in 1957, with neon ions in 1979, and with carbon ions in 1994. Early clinical experience showed that hadrontherapy is beneficial in the treatment of base of skull and spinal tumors, as well as ocular melanoma, and that it is potentially advantageous for other cancer sites, including prostate, lung, liver, esophagus, and head and neck. Initially, treatment was performed in the physics research centers offering some time for clinical use. At present, the most frequently used hadrons are protons and carbon ions, although in the case of the latter this is still on an experimental basis. Others include neutrons (although their limitations are now apparent) and nuclei of light atoms such as helium, oxygen, and neon, which at present are mainly of historical interest. All these particles have either the physical advantage of better spatial selectivity (improved dose distribution) or a higher radiobiological efficacy than that of photons, or both.

### RADIOBIOLOGY

The radiobiological characteristics of hadrons differ from those of photons and offer a theoretical advantage over photons in overcoming radioreistance because of the difference in the relative biological effects between tumor and normal tissue. Relative biological efficacy (RBE) is defined as the ratio between the dose of the reference photon radiation required to produce a certain reaction and the dose of particle beam necessary to have the same effect (eg, skin and mucosal reactions). A smaller physical dose of hadrons than megavoltage photons is needed to produce a similar reaction.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Neutrons</th>
<th>Protons</th>
<th>Ions</th>
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<tr>
<td>RBE</td>
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<td>1.1-1.3</td>
<td>1.25-4.5</td>
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Abbreviations: LET, linear energy transfer; RBE, relative biological efficacy. *Mass is expressed in MeV/c^2.*

### PHYSICS

Protons have physical characteristics that differ from those of photons. They permit improved sparing of critical organs due to the particular ballistic of protons, in which with dose deposition is limited mainly to the so-called Bragg peak, which can be spread out. Thus, the integral dose is low, and the treatment is extremely conformal to the target volume.

Fast neutrons (neutrons in the megavoltage range) have a similar exponential dose deposition in depth to that of megavoltage X-rays. However, they can be clinically useful because of their high...
biological effect due to the high LET, which produces a high RBE reaching a value of 3.0 to 3.3.2

The advantages of ion therapy include spatial selectivity related to a Bragg-peak similar to that of protons and a very sharp lateral penumbra. They also have a high radiobiological efficacy with RBE varying from 1.25 for helium to 4.5 for neon. These characteristics make ions the most attractive modality for radiation treatment of radioresistant tumors close to critical structures.

In recent years, great advances have been made in the delivery and verification of radiotherapy with photons, the technique of IMRT (intensity modulated radiotherapy) being the most promising. A planning exercise for IMRT comparing photon and proton beams showed that both treatments achieve an equally homogeneous coverage of the target volume, however the dose administered to the critical organs using protons was lower than for the photon radiotherapy.15,16 This makes possible to deliver equivalent tumor doses 15% to 30% higher than those that can be delivered with standard X-ray therapy, so improved higher local control and/or survival can be expected.10 Obviously, the precise deposition of energy with an extremely low dose outside the target requires precise identification of the target itself.17,18

In conclusion, the ideal indications for using hadrontherapy are radioresistant tumors, located near highly radiosensitive critical organs, when the main problem with conventional radiotherapy is local control and the risk of distant metastasis is low.6 This is the case for many head and neck malignancies.

FACILITIES
Although particle beam therapy offers numerous potential advantages, it is carried out in only a few facilities throughout the world because of its expense and complexity.19 In the past, treatment was performed in non–hospital-based centers, using fixed energy beams that are not ideally suited for clinical use. Moreover, the time allowed for patient access was very much restricted as priority was given to physics research programs. Recently, together with the availability of improved radiotherapy planning, delivery, and verification systems, more attention has been paid to this form of irradiation. Consequently, several dedicated facilities with particle accelerators have been developed in the United States, Japan, and Europe.

Neutron therapy was developed in a few centers in the United States and Europe over several decades of the last century, from the 1930s to the 1980s, but no new facilities for external beam neutron radiotherapy have been scheduled in recent years.

The clinical use of proton therapy began in 1954 at the Lawrence Berkeley Laboratory (LBL) in California and at Uppsala University, Sweden, then in 1961 at the Harvard Cyclotron Laboratory (HCL) in Cambridge, MA. The first hospital-based facility began its activity in 1990 at the Loma Linda University Medical Center (LLUMC) in California. At present, 22 proton therapy centers are active worldwide and 15 are planned for the next few years. Proton therapy has been used for about 40,000 patients worldwide so far (Table 2).20 A more recent development for proton therapy involves the beam delivery system that has changed over time from passive to active scanning in order to spread out the Bragg peak and obtain a better dose distribution to the target. The main part of this development was done at the Paul Scherrer Institut (PSI), Switzerland, where the proton IMRT has recently been implemented.15

The first center for ion therapy was the LBL in California, which was started in 1957, using mainly neon and helium ions. The new facilities employ carbon ions,4,6,21 which are currently available at 3 centers worldwide: 2 hospital-based facilities in Japan (the National Institute of Radiological Sciences [NIRS] in Chiba and the Hyogo Ion Beam Medical Center in Hyogo, Japan), and 1 basic physics institute in Germany (Gesellschaft fur Schwerionenforschung [GSI] in Darmstadt).6 More than 1800 patients have been treated since 1994 with carbon ion beam at NIRS in Chiba and about 200 patients have been treated with the carbon ion beam at GSI in Darmstadt since 1997.6

Owing to the limited availability of particle beams and its complex quality assurance requirements, some patients were treated with mixed beam including some fractions of photon therapy and some using particle beams.12,22 For the same reasons, hypofractionated (using higher dose per fraction) schemes are employed to reduce the number of treatment sessions.

ECONOMICS
The cost of radiotherapy is generally lower than the cost of any other type of therapy for malignant diseases.3 According to some cost-of-treatment analyses, the cost of hadrontherapy is higher than con-
ventional radiotherapy and depends on the type of particles used. The cost of proton therapy is still 2 to 3 times higher than that for photon techniques, but the gap is decreasing as the availability of commercial proton machines increases and there is a rise in the cost of new machines dedicated to stereotactic and IMRT techniques. The cost of light ions is about 2 to 3 times higher than for proton therapy. The high cost of hadrontherapy is largely due to the cost of cyclotrons and synchrotrons. It is even more difficult to accelerate ions, which are heavier than protons (and require high-energy synchrotrons). However, according to Brahme's assessment, the cost-effectiveness of light ions per patient cured does not differ substantially from that of advanced conventional radiation therapy.
An extensive review of the clinical applications of hadrons has been published elsewhere. In this article, we present the review of potential benefits and early clinical experience with hadrons for head and neck malignancies. An overview of the indications and treatment schemes is also given.

MATERIALS AND METHODS
References for this review were identified by a comprehensive search on MEDLINE for 1980 to 2005. The keywords included hadrontherapy, ion therapy, proton therapy, particle beam therapy, neutrons, head and neck malignancies, head and neck tumors, and head and neck cancer. References were supplemented with relevant citations from older literature and from the reference lists of the consulted papers. Papers were selected on the basis of their relevance to the topic. Data presented in the form of an abstract or in language other than English were included when they added significant information.

RESULTS
General Indications. Historically, neutrons were the first hadrons used in clinical studies in centers equipped with a cyclotron. A number of tumors were treated with controversial results. Phase III trials performed in the 1980s suggested to conclude that neutrons are indicated for salivary and advanced prostate carcinomas. During the past decade, neutron therapy has been limited to certain tumor sites (salivary glands, paranasal sinus, some bone and soft tissue sarcomas) because of the high risk of late damage to surrounding tissue. This high rate of late complications is a result of the low spatial selectivity and high RBE of neutrons. A different approach to neutron therapy is boron neutron capture therapy (BNCT) explored for the first time in the 1950s. The use of BNCT has been investigated only in certain tumors, such as glioblastomas and melanomas. Promising results have been recently reported in head and neck malignancies.

Clinical Experience in Head and Neck with Regard to Tumor Site
Skull Base Chordoma and Chondrosarcoma. Charged particle therapy such as therapy with protons or helium ions is highly effective in controlling lesions arising in the skull base, such as chordoma and chondrosarcoma. The widest experience in the use of particle therapy for skull base tumors regards proton therapy, which can be considered standard treatment in this type of tumor. Chordomas and chondrosarcomas are very close to dose-limiting structures such as optic pathways, brainstem, and spinal cord. Local failure is the main reason for relapse in chordomas as distant metastases.
rarely occur. Conventional radiotherapy after surgery provides 5-year progression-free survival within the range of 17% to 33% for chordomas at all sites.\textsuperscript{35–38} Five-year survival in the patients with skull base chondrosarcoma ranges from 43% to 90%.\textsuperscript{39–42} Better results have been reported for stereotactic radiotherapy.\textsuperscript{43,44}

The aim of proton beam radiation therapy is to improve local control by using higher radiation doses. A series of 621 cases of chordoma and chondrosarcoma of the base of skull treated at the Massachusetts General Hospital (MGH) in Boston to a total dose ranging from 66 to 83 GyE showed local control at 10 years of 54% and 94%, respectively, for chordoma and chondrosarcoma, with a low late toxicity rate.\textsuperscript{45} In all cases, surgery was performed before radiotherapy to debulk the tumor and obtain a favorable geometrical configuration. The series treated at LLUMC was published by Hug et al.,\textsuperscript{46} who reviewed the results in 58 patients treated with proton therapy to a total dose of 65 to 79 GyE after surgical resection. Local control and overall survival at 5 years were obtained in 59% and 79%, respectively, for chordoma and 75% and 100% for chondrosarcoma. The experience at the Centre de Protontherapie d’Orsay (CPO) in France for 67 cases of operated skull base chordoma and chondrosarcoma treated to 60 to 70 GyE showed a 3-year local control and 4-year overall survival of 71% and 88%, respectively, for chordoma and 85% and 75% for chondrosarcoma.\textsuperscript{34}

Ion therapy was used to treat neoplasms originating in the base of skull for the first time at LBL.\textsuperscript{10} In about 200 patients treated with helium and neon ions to an average dose of 65 GyE, the rate of local control at 5 years was 85%, 78%, and 63%, respectively, for meningioma, chondrosarcomas, and chordoma. The study confirmed the greater risk of late central nervous system effects with high-LET irradiation, in particular in the subgroup of patients treated before 1986 (the rate of serious late complications was 41%). It has been reduced to about 20% for those irradiated between 1987 and 1992 as a result of the improvement in planning techniques and dose delivery.

At the GSI in Darmstadt, 37 patients with chordomas (n = 24) and chondrosarcomas (n = 13) were treated with carbon ion radiotherapy within a phase I/II trial from 1998 to 2000.\textsuperscript{47} All patients with low-grade chondrosarcomas and 22 of 24 with chordomas had local disease control after 2 years. Two-year progression-free survival was 100% and 83%, respectively, for chondrosarcomas and chordomas. Treatment-related toxicity was mild. A recent update on 152 patients confirmed the results with actuarial 3-year local control of 81% for chordomas, 100% for chondrosarcomas, and 62% for adenoid cystic carcinomas with no grade 4 to 5 toxicity.\textsuperscript{6}

**Salivary Gland Tumors.** The treatment of advanced salivary gland tumors with conventional radiotherapy is not satisfactory due to the low radiosensitivity of these malignancies. The first study of particle beam therapy included neutron therapy in the 1930s at the University of California LBL.\textsuperscript{5} Initial experience showed promising results in patients with inoperable, not completely resected, or recurrent adenoid cystic tumors.\textsuperscript{48} During the 1980s, a randomized study of the Radiation Therapy Oncology Group and the Medical Research Council (RTOG-MRC trial) showed a benefit in terms of local control for the patients treated with neutron beam when compared with those treated with photon therapy.\textsuperscript{49} Although a significant improvement in local control was observed (56% vs 17%), long-term survival rates showed no difference, mainly due to a high incidence of distant failure.\textsuperscript{50}

These benefits were later reported in several nonrandomized series\textsuperscript{5,11,48,51–59} and in pooled European studies.\textsuperscript{60} All these studies showed consistently better local control with neutron beams than with mixed beam or photons only (75% at 5 years vs about 30%). A small tumor size (< 4 cm) was associated with an excellent locoregional control.\textsuperscript{61} Once more, some series show that, despite high locoregional control rates, overall survival rates remain the same due to a high rate of distant failure. This pattern of failure definitively calls for better systemic therapy in salivary gland tumors. Both good local control and normal tissue reactions with neutron therapy can be explained with high LET and RBE of neutrons.\textsuperscript{5,6} Relatively high rates of severe late effects (in particular, in the postoperative setting) have been reported in some series.\textsuperscript{28,57,62,63} Modern neutron machines and the use of 3D treatment planning systems are now available and may further reduce side effects.\textsuperscript{60} Some series are limited to the adenoid cystic carcinomas\textsuperscript{52,64}, however, most likely the benefit regards all salivary gland tumors. Interestingly, an overall local control rate of 100% (at the 4.5-year follow-up) was observed in 6 patients treated with neutron therapy for recurrent pleomorphic adenoma of the parotid gland.\textsuperscript{65} Results that are superior to those for photon therapy, with a 5-year disease-specific survival and local failure rates of
59% and 61%, respectively, were also reported in a series of 18 patients treated with neon ions for recurrent or macroscopic salivary gland carcinomas including various sites and histologies. In another report from the LBL, the results were seen to be worse for minor salivary gland tumors, especially in locally advanced disease infiltrating the skull base.

The effectiveness of neutrons and neon ions in salivary gland tumors has prompted ongoing clinical trials with carbon ions. Carbon ion therapy may reduce toxicity because of its improved dose distribution, while still achieving higher local control due to a higher RBE than in the case of photons. Promising results were found in a dose escalation study including 21 patients with locally advanced adenoid cystic carcinoma without a history of previous irradiation. The patients were treated at GSI in Darmstadt with stereotactically guided or photon IMRT (45–54 Gy with 1.8-Gy daily fractions) and a carbon ion boost of 18 GyE, given with 6 weekly fractions of 3 GyE. After median follow-up of 14 months, actuarial overall survival and locoregional control were 75% and 62%, respectively. The results are similar to those obtained with neutrons alone but with lower late toxicity. In the study of Mizoe et al., 5-year local control of 100% was reported in 8 patients treated with carbon ion therapy for salivary gland carcinoma at NIRS. The relatively high local control obtained with carbon ions and neutrons can be explained by the similar radiobiologic properties of these particles. Compared with neutron radiotherapy, carbon ion beams also provide better physical selectivity, leading to a reduction in complications to normal tissue.

**Pharynx.** Of the pharyngeal tumors, the nasopharynx has been explored the most in clinical studies by particle beam radiotherapy because the vicinity of normal nervous tissue limits the dose in photon radiotherapy. In the comparative treatment planning study of Brown et al., the use of protons resulted in a more even distribution of dose to the tumor, a reduction in dose to adjacent tissue and consequently a tumor dose escalation (of about 8%), relative to conventional photon radiotherapy. Similarly, treatment with mixed beams (photon and protons) resulted in better tumor coverage compared with conventional photon therapy in the study of Noel et al. Since proton therapy is more expensive and time consuming than conventional photon radiotherapy, it should be considered in highly selected tumors, ie, in the case of extensive skull base involvement or recurrence after photon radiotherapy.

Promising results were found in the dose escalation study on carbon ions in locally advanced head and neck cancer including pharyngeal tumors treated at the NIRS in Chiba. There is an ongoing phase I/II study using proton therapy for squamous cell oropharyngeal carcinoma sponsored by the American Proton Radiotherapy Oncology Group (PROG).

**Nasal and Paranasal Sinuses.** Hadrons may also offer attractive dose localization for the irradiation of paranasal sinus tumors, especially ethmoid and sphenoid sinus malignancies. Two-year local control and survival of 44% and 38%, respectively, were reported in patients with advanced squamous carcinoma of the maxillary antrum treated with neutrons. Recently, the rapid regression of large, unresectable, previously irradiated undifferentiated sinonasal carcinoma after a single fraction of BNCT was reported. On the basis of this experience, a phase I study on BNCT for inoperable, locally advanced, previously irradiated head and neck cancer has been initiated in Finland.

The complete and partial response rates of 75% and 25%, respectively, were observed in 20 patients treated with combined photon/proton beams for paranasal carcinomas. Comparative treatment planning studies demonstrated a significant advantage in using protons rather than photons even with IMRT technique. In the group of 12 paranasal sinus cancer patients treated with neutron ions at the LBL, disease-specific survival and local control rates at 5 years were 69%. When compared with the historical results, the LBL series suggests that neon ion treatment improves outcome in paranasal sinus tumors. More recently, 10 cases with locally advanced disease were reported in a larger review article on ion therapy results from NIRS. Local control was obtained in 49% at 5 years, demonstrating that ion therapy is able to obtain regression of disease with long-term potentially favorable results.

**Malignant Melanoma.** The first experience of neutron radiotherapy in the treatment of melanoma was performed at Hammersmith Hospital and reported by Catteral et al. Since proton therapy is more expensive and time consuming than conventional photon radiotherapy, it should be considered in highly selected tumors, ie, in the case of extensive skull base involvement or recurrence after photon radiotherapy.
local recurrence. In the series reported by Linstadt at LBL, local control was obtained in 2 of 6 patients treated with neon ions for melanoma located in a variety of sites including paranasal sinus, esophagus, and skin. Promising results were found in a recent dose escalation study on carbon ions at NIRS. Five-year local control of 5 mucosal melanoma patients presenting with gross tumor was 100%. 

Varia. Some investigators report on the head and neck cancer population without distinguishing the subsite (due to small patient numbers). 

A randomized RTOG trial comparing mixed photon and neutron beams with photons alone for unresectable squamous cell carcinomas of the head and neck showed no difference in local control or overall survival, although neutrons did produce a significant improvement in the complete response rate of metastatic neck nodes. 

Overall 5-year survival and local control rates of 44% and 74%, respectively, were observed in the group of 33 patients with head and neck malignancies treated with proton beams to a median dose of 76 Gy at the Tsukuba Proton Medical Research Center in Japan. In the dose escalation study on carbon ions in the group of 34 patients with locally advanced head and neck cancer, the local control rate was 75% at 5 years. 

Low incidence of late skin and mucosal reactions invite the investigators to continue their trial. 

In the group of 88 patients, better results with ion therapy were observed in patients with nonsquamous cell histotypes (eg, melanoma, adenoid cystic carcinomas). In some series, this can be partially explained by the inclusion of patients with very locally advanced disease, treated mainly within feasibility protocols (in order to study treatment technique and toxicity). 

Some rare head and neck malignancies, such as lacrimal gland cancers, glomus tumor, soft tissue and bone sarcomas, laryngeal sarcomas, and tracheal carcinoma, were also treated with hadrontherapy. Particularly good results were observed in primary and recurrent sarcomas of head and neck treated with combined photons and protons. Such results were attributed to the selectivity of proton dose distribution. Hadrontherapy was also employed in a few cases of carcinomas of the thyroid gland, pituitary tumors, skin, ear, and cervical esophagus. However, the numbers are still too low to draw any conclusion about the efficacy of particle beam therapy in these patients. Interestingly, a 5-year local control of 100% was reported for 4 patients treated with carbon ion therapy for ear carcinomas. Also, the results of carbon and neon ion therapy for bone and soft tissue sarcomas at different sites appear to be better than the results achieved with conventional photon radiotherapy.

DISCUSSION

The review of the literature shows few reports on particle beam radiotherapy for head and neck malignancies. This form of radiotherapy is definitely more complex and expensive than conventional photon radiotherapy and is not yet widely available. Therefore, most reports are retrospective and include a small number of patients with different types of malignancy. The review shows the potential clinical benefits of particle beam therapy as a result of its physical selectivity (better dose deposition for protons and ions) and radiobiological efficacy higher than that of photon radiotherapy (especially for neutrons and ions). Consequently, this treatment should be considered in the case of radioresistant tumors located near highly radiosensitive normal tissue. Skull base tumors are a well-established indication for proton therapy. More recently, ion therapy has been favorably explored for these tumors. Sino-nasal and nasopharyngeal tumors are also potentially indicated for hadrontherapy. Whenever possible, comparison should be made between treatment plans for the 2 treatment modalities. Hadrontherapy should be considered when this comparison confirms the superiority of charged particles. Hadrontherapy should not be proposed if the results obtained with conventional photon megavoltage therapy are satisfactory (eg, small tumors of nasopharynx, glottic tumors).

There are still many aspects of hadrontherapy that must be explored. The development of new facilities offers the possibility of performing more extensive clinical studies (several randomized trials have been recently launched). The improvements necessary to fully exploit the potential of these facilities include further optimization of treatment planning, delivery, and verification. These improvements, together with better tumor identification using computed tomography (CT) scanning, magnetic resonance imaging (MRI), and nuclear medicine examinations such as posi-
tron emission tomography (PET), may continue to reduce the level of serious complications and increase local control and survival rates. Optimization of the dose fractionation-to-volume relationship is warranted. Moreover, individualized predictive assays may prove useful to define growth parameters and inherent radiosensitivity to high-LET radiotherapy. The continuous study of histology and growth kinetics correlated with clinical results is fundamental in defining the patient population that may receive the greatest benefit from particle beam therapy. Therefore, future research on hadrontherapy for head and neck tumors should focus on the technical, clinical, radiobiological, and molecular aspects to optimize dose and fractionation on one side and explore in greater depth the most effective combination with surgery and possibly with chemotherapy.

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REFERENCES


