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The Treatment of Chordoma and Chondrosarcoma of the Skull Base with Particular Attention to Radiotherapy

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Abstract

Chordoma and Chondrosarcoma are rare, locally aggressive, tumors occurring in one third of cases in the base of the skull. Although the risk of distant metastasis is low, without adequate therapy, these tumors often recur locally with significant morbidity and mortality. The mainstay of treatment is maximal tumor debunking. A gross total resection, however, is difficult to achieve, often leaving residual tumor. Adjuvant radiation is considered a standard therapeutic option postoperatively to reduce the risk of local recurrence and increase survival. High doses of radiation are required, as these tumors are considered relatively radioresistant but the presence of several organs at risks a major challenge with respect to covering the target with the prescribed high dose. In this regards, protons, for their physical and dosimetric advantages, have become a standard of care. Even though some reports have shown clinical activity with the use of chemotherapy or biologic drugs, there is no role at the moment for medical treatment.

Introduction

Chordoma (Ch) and Chondrosarcoma (Chs) are rare tumors; Ch arise from the primitive notochord [1], whereas Chsare malignant primary bone tumors of cartilaginous origin; they can resemble Ch and are often misdiagnosed as such [2]. Ch and Chs are low-grade malignancies that in about one third of cases occur at the skull base, particularly developing in the clivus, with alocally invasive spread. Their incidence is less than 0.1 per 100,000 per year [3]. Chondrosarcoma is less common than Ch, particularly in the skull base location. In combined series, the occurrence is typically one-half to one-third the frequency of Ch. Chordoma and Chondrosarcoma have been historically grouped together in retrospective and prospective series because of their rarity and similar midline presentation, similar imaging characteristics, and possible confusion in initial pathology. However, these lesions are distinct clinic-pathological entities and can vary significantly in outcome [4]. In particular Ch is highly recurrent, making its clinical progression very similar to that of malignant tumors. Because metastasis and dissemination are uncommon, local control by aggressive treatment is crucial for long-term survival. Unfortunately, these lesions grow next to structures deputed to relevant physiologic functions such as temporal lobes, brainstem, cranial nerves, major vessels, pituitary gland etc. that limit extensive surgical approaches and delivery of definitive doses of radiotherapy without severe risks of side effects and complications. The aim of the treatment is to avoid serious damage to the surrounding brain parenchyma and cranial nerves and to relieve any compression caused by the tumor [5]. The most recent progresses of surgery and radiotherapy requiring a special expertise have permitted to improve the results in terms of local control with acceptable risks.

Surgery

Surgical resection remains the first choice for Ch and Chs of the skull base with the appropriate surgical approach based on tumor size and location. Given the irinvasive nature with spread along critical bony and neural structures, and large tumor burden, complete resection of these tumors is often difficult. Surgery should aim towards maximally safe cytoreductive surgery with wide en-bloc resection with preservation of neurological function and quality of life, even at the price of postoperative residual tumor. Within the constraints to safety and minimizing complications, a particular effort should be made to obtain the maximal surgical reduction of the lesion and clearance from eloquent structures even to repeating further surgery. The reduction of the burden of tumor and the abutting to critical structures can also favor the safer delivery of high doses of irradiation. These lesions have a broad surgical approach strategy that is based on the location of the tumor and the surgeon's preference: in the literature surgical goals and approaches selected

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Table 1: Series of skull base chordoma and chondrosarcoma treated by proton beam therapy.

Authors [year]	Histology	N. of Patients	Mean total dose (range) [Gy (RBE)]	Dose per fraction [Gy(RBE)]	Mean follow up [months]	Local control [%]	Overall survival [%]
Hug et al. [32]	Chordoma	33	71.9 (66.6-79.2)	1.8	33.2 (7-75)#	59 (5 y)	79.0 (5 y)
	Chondrosarcoma	25	69.3 (64.8-72)	1.8		75 (5 y)	100 (5 y)
Munzenrider et al. [27]	Chordoma	290	66-83#	1.8-1.92	41 (1-254)#	73 (5 y), 54 (10 y)	80 (5 y), 54 (10 y)
	Chondrosarcoma	229		1.8-1.92		98 (5 y), 94 (10 y)	91 (5 y), 88 (10 y)
Noel et al. [28]	Chordoma	34	66.7 (60-73)#	1.8-2.0	31*	83.1 (3 y)	91.2 (4 y)
	Chondrosarcoma	11		1.8-2.0		90 (3 y)	60 (4 y)
Noel et al. [33]	Chordoma	100	67	1.8-2	31	53.8 (4 y)	80.5 (5 y)
Igaki et al. [34]	Chordoma	13	72.0 (63-95)	2.0-3.5	69.3*	66.7 (5 y)	44.2 (5 y)
Ares et al. [35]	Chordoma	42	73.5 (67-74)	1.8-2.0	38#	81 (5 y)	62 (5 y)
	Chondrosarcoma	22	68.4 (63-74)	1.8-2.0		94 (5 y)	91 (5 y)
Fuji et al. [36]	Chordoma	8	63 (50-70)#	1.8	42*	100 (3 y)	100 (3 y)
	Chondrosarcoma	8		1.8		86 (3 y)	100 (3 y)
Yasuda et al. [37]	Chordoma	40	68.9 (55-74)	N/A	62.3	70 (5 y)	83.4 (5 y)
Deraniyagala et al. [38]	Chordoma	33	77.4 – 79.4	1.8	21	86 (2y)	92 (2 y)
Grosshans et al. [39]	Chordoma	10	69.8 (68-70)	2.0	27 (13-42)#	82 (2 y)	100 (2 y)
	Chondrosarcoma	5	68.4 (66-70)	2.0		100 (2 y)	100 (2 y)
Weber et al. [29]	Chordoma	151	72.5# (70.3-74.7	1.8-2.0	50 (4-176)#	75.8 (5 y), 70.9 (7 y)	86.4 (5 y), 80.0 (7 y)
	Chondrosarcoma	71		1.8-2.0		93.6 (5 y), 93.6 (7 y)	93.6 (5 y), 93.6 (7 y)

RBE*: Median; N.: Number; #: Ch and Chs together, y: years; N/A: Not Available; Gy: Gray; RBE: Relative Biological Effectiveness

on a case-by-case basis. Transphenoidal, transanal, trans maxillary, anterior cervical retro pharyngeal, and transanal approaches have been well documented [6]. Surgical results and clinical outcomes have improved throughout the years [7]. A variety of both open and endoscopic therapeutic approaches have evolved, with an emphasis on neurological preservation, increasing the rate of gross total resection and reducing morbidity. To exploit a total resection can be challenging because of difficult access, anatomic constraints, infiltrative nature of the lesion, and proximity to critical structures such as optic nerves, optic chiasm, cranial nerves, cochlea, brainstem, pituitary gland, and temporal lobes. Lateral extension of the disease often can be accessed with endoscopic nasal approaches [8]. The most challenging side effect with endoscopic approaches is the defect closure and prevention of Cerebrospinal Fluid (CSF) leak. With the increased experience with endoscopic skull-based techniques, improved instrumentation, and, if needed, the use of arterially based mucosal flaps for cerebrospinal fluid leak closure, the ability to approach resections of these lesions has significantly improved [9-12] permitting more thorough removal of tumor with less postoperative morbidity. Local Recurrence (LR) with surgery alone has been found very high (>50%) mainly in Chand can be associated with significant morbidity [13]. Chondrosarcoma appear to be more indolent than chordomas, which may lead to favoring a more conservative initial surgery. Some small tumors and other select cases may be addressed with observation alone if of low-grade. In these cases, residual tumor can be observed closely without adjuvant treatment; being local recurrence rates and ability to metastasize less than Chordoma.

Considering the high rate of LR, postoperative radiotherapy plays a very important role in a global therapeutic approach; however, there is currently no clear consensus on the post-surgical radiation treatments that should be used after maximal resection.

Patients sometimes can subsequently develop recurrent disease along the cervical skin incision due to surgical seeding: tumor seeding can occur anywhere along the operative route and is often outside the field of radiotherapy [14] even though the frequency of this occurrence is reported in less than 5% of cases and the need to include it in the radiotherapy field is controversial [15]. The use of novel clean oncologic techniques to minimize exposure may help limit tumor seeding.

Radiotherapy

Considering the difficulty to obtain a gross total resection and wide surgical margins, adjuvant Post-Operative Radiotherapy (PORT) is important or even essential for local tumor control even in these slowly growing tumors. In retrospective series aggressive up-front management with immediate PORT after surgery showed a 10-year survival rate of 65% versus 0% in comparison to those patients treated with RT at the time of recurrence [16].

The control of these radioresistant tumors requires doses more than 56-70 Gy, the dose level usually administered with photon beams. Doses of at least 74 Gy using conventional fractionation (1.8-2 Gy per fraction) that are beyond the tolerance of several critical structures are recommended [17,18]. This makes the treatment with X-ray difficult and the 5-year Progression Free Survival (PFS)

Table 2: Series of skull base chordoma and Chondrosarcoma treated by carbon ions.

Authors [year]	Histology	No. of Patients	Mean total dose (range) [Gy (RBE)]	Dose per fraction [Gy(RBE)]	Mean follow up [months]	Local control [%] (range)	Overall survival [%] (years)
Mizoe et al. [43]	chordoma	33	48 – 60.8	3.4 – 4.2	53 (8-129)	85.1 (5 y), 63.8 (10 y)	87.7 (5 y), 67 (10 y)
Uhl et al. [44]	chondrosarcoma	79	60	3	91 (3-175)	88 (5 y), 88 (10 y)	96.1 (5 y), 78.9 (10 y)
Uhl et al . [41]	chordoma	155	60 (54-70)	3	72 (12-165)	72 (5 y), 54 (10 y)	85 (5 y), 75 (10 y)

RBE*: Median; N: Number; #:Ch and Chs together, y: Years; Gy: Gray; RBE: Relative Biological Effectiveness

Table 3: Series of skull base chordoma and chondrosarcoma treated by Intensity Modulated Radiation Therapy (IMRT) or Stereotactic Radiation Therapy (SRT).

Authors [year]	Histology	N.of Patients	Mean total dose (range) [Gy]	Dose per fraction [Gy]	Mean follow up [months]	Local control [%]	Overall survival[%]
Debus et al. [49]	chordoma	37	66.6	1.8	95	50 (5 y), 40 (8 y)	82 (5 y)
	chondrosarcoma	8	64.9	1.8	59	100 (5 y)	100(5 y)
Foweraker et al. [45]	chordoma	9	65 (62-65)	1.8-2.0	34	88(5 y)	62(5 y)
	chondrosarcoma	3	60-65	1.8	17.5-107.5	100 (5 y)	100 (5 y)
Hong Jiang et al. [48]	chordoma	10	N/A	N/A	17	100 (2 y)	100 (2 y)
Hauptman et al. [54]	chordoma	13 (5 SRS)	70 (53-84)	2.0	44	50 (5 y)	82 (5 y)
	chondrosarcoma	2	68-70	2.0	7-62	100 (5 y)	100 (5 y)
Potluri et al. [46]	chordoma	13	65 (62-70)	1.8-2.0	53	83 (5 y)	92 (5 y)
	chondrosarcoma	6	62.5 (60-65)	1.8-2.0	53	100 (5 y)	100(5 y)
Ahmed et al. [50]	chordoma	30	81	1.2-1.5 BID	76	31 (5 y)	73 (5 y), 44 (10 y),
Bugoci et al. [51]	chordoma	12	66.6 (48.6-68.4)	1.8	42	37.5 (5 y)	76(5 y),

Gy: Gray; N: Number; N/A: Not Available; y: Years; SRS: Stereotactic Radio Surgery; BID: twice daily

reported with X-ray treatment is poor in the range of 17-39% [19-22]. It is to note that most current series studying long-term outcome with conventional radiation therapy employed older techniques and may not apply to current management.

Advances in radiation technology and delivery with the introduction of hadrons (i.e., protons or charged particles, including carbon ions, helium, or neon) have led to higher doses being delivered to the target, with limited injury to the surrounding tissue and improved radiobiological effect. Unfortunately, the availability of hadron-based therapy is limited because of the associated construction and operational expenses [23,24].

Particles

In comparison with conventional radiotherapy, particle beams such as Proton Beam Therapy (PBT) and Carbon Ion Radiation Therapy (CIRT) have different physical and biological characteristics with better dose distribution. They deliver a lower entry dose, depositing the majority of their energy at the end of their path, yielding atypical narrow dose energy peak called “Bragg peak”. This steep fall-off allows for delivery of high doses and sparing of tissue beyond the tumor. In the skull base, this feature is crucial, given the presence of several critical structures at risk.

Because of this physical property, particles are suitable for treating skull base tumors because high doses can be delivered to the target while preserving the surrounding normal tissue. In addition, because it is possible to make irregular target fields, they can deliver uniform doses to irregularly shaped tumors. Proton beams are categorized as low Linear Energy Transfer (LET) radiation with a biological effect of 1.1 times that of photon beams [25]. Radio biologically, carbon-ion beams result in two to three times the Relative Biological Effectiveness (RBE) of proton and conventional irradiation methods and they may be effective for treating highly radioresistant tumors [26].

Proton beam therapy (PBT)

PBT was shown to be superior to photons in the seminal report of the Boston group for delivering higher doses to the tumor while keeping lower doses to normal tissues in the clival region [27]. In this early study at Massachusetts general Hospital in Boston (US) and at the institute Curie at Orsay (France) [28], PBT was often conducted in combination with photon radiotherapy. Afterwards, PBT has been considered the irradiation technique of choice in the treatment of these tumors and adjuvant therapy with Ch and Chs is largely accomplished with proton EBRT, despite the limited number of available centers, but its exact role has not been fully established [17,18]. New delivery techniques have developed and the recent introduction in the clinic of spot scanning PT technique (single pencil proton beams that can be modulated or conformed) to mimic current photon technique (i.e., IMRT) can offer very exciting results with high long term late grade >3 toxicity-free survival [29].

Proton therapy has been used also in pediatric patients mixed with photons [30] or alone [31]. In these series, even with a limited number of patients, the treatment was well tolerated in children allowing excellent local control with minimal long-term toxicity.

At the moment, instead of the number of published series showing a very satisfactory local control rate achieved with protons, high level evidence for unequivocal recommendation does not exists [32]. The results of PBT reported in the literature are shown in (Table 1).

Table 4: Series of skull base chordoma and chondrosarcoma treated by Stereotactic Radio Surgery (SRS).

Authors [year]	Histology	N.of Patients	Mean total dose (range) [Gy]	Dose per fraction [Gy]	Mean follow up [months]	Local control [%]	Overall survival[%]
Gwak et al. [55]	chordoma	7	21-43.6	7-8.7	20 (12-32)	6/7 controlled	86 (2 y)
	chondrosarcoma	2	30-43. 6	8.7-10	11-33	272 controlled	N/A
Hasegawa et al. [57]	chordoma	27	14 (marginal)	SF	59	80 (5 y), 56 (10 y)	72 (5 y), 72 (10 y)
	chondrosarcoma	7				86 (5 y)	86 (5 y)
Martin et al. [58]	chordoma	18	16.5	SF	88	62.9 (5 y)	62,9 (5 y)
	chondrosarcoma	10			86	80 (5 y)	N/A
Liu et al. [60]	chordoma	31	12.7 (marginal)	SF	30	21.4 (5 y)	21.4 (5 y)
Henderson et al. [56]	chordoma	7	35 (28-40)	7-7.5	83 (12-216)	6/7 controlled	86 (5 y)
Dassoulas et al. [59]	chordoma	43	15 (marginal)	SF	70	50.3	N/A
Ito et al. [55]	chordoma	10	17.8 (12.5-20)	SF	71	47.9 (5 y)	89.5 (5 y)

Gy: Gray; N: Number; N/A: Not Available; y: Years; SF: Single Fraction

Carbon ion radiation therapy (CIRT)

In addition to proton therapy, heavy ion beams have been used for the treatment of skull base Ch and Chs and its use has been increasing, especially in Europe and Asia [33]. Heavy ions, most frequently carbon ions, have been theoretically postulated to have a biological advantage in terms of Relative Biological Effectiveness (RBE) over photon and proton therapy, particularly in slow-growing, usually radio resistant, tumors.

The long-term results of irradiation with carbon ions using a raster scanning technique in patients with skull base Ch has been recently published [34]. A total of 155 patients were treated; at a median follow-up of 72 months, 5 and 10-year LC rates were 72% and 54%, respectively, whereas the 5-year - 10-year OS rates were 85%, and 75%, respectively. CIRT has been proposed also as a method of re-irradiation in cases with tumor recurrences with satisfactory outcome (survival after re-irradiation 86% at 24 months, and 43% at 60 months) [35]. Moderatehypofractionation with 16-22 fractions of 3- 4.2 [36] GyE per fraction is feasible [37]. The results of patients with CH or CHS of the base of the skull treated with carbon ions are reported in (Table 2).

Modern photon radiation therapy (RT)

Recent development of photon radiotherapy has enabled to achieve a co focal and precise dose distribution with different irradiation photon techniques [38-44]. The results obtained with these advanced, modern forms of radiotherapy, even though in limited sample of patients, are reported in (Table 3 and 4).

Conformal radiotherapy and intensity modulated radiation therapy (IMRT)

Relatively high doses (60-65 Gy) were delivered with conformal modern techniques using a combination of static fields and arcs with advanced planning techniques showing satisfactory results even though in a very limited sample [45]. Similar dose (65 Gy in 39 fractions) was used in the report of Potluri et al. [46], resulting in a survival rate for radically treated patients with chordomas of 92% and a 5 year local control rate of 83%. The 5 year cause-specific survival and local control rates with Chondrosarcoma were both 100%.

Intensity modulated radiation therapy (IMRT) is the new paradigm of treatment in radiotherapy [47] and has been applied to few series. Hong Jiang et al. [48] published on 10 patients treated with IMRT after an endoscopic resection in clival tumors; even though no technical data on irradiation were available and a limited follow-up was reported, postoperative IMRT was referred as an effective adjuvant treatment.

Stereotactic radiation therapy

Stereotactic treatments can be delivered either of a single fraction (stereotactic radiation surgery - SRS) or in a limited number of sessions usually between 3 and 5 (stereotactic radiation therapy - SRT).

A. Stereotactic radiotherapy – SRT

Fractionated Stereotactic Radiation Therapy (SRT) delivered at a median dose of 66.6 Gy (for Ch) and 64.9 Gy (for Chs) showed to be feasible and safe [49]. Local control at 5-years of 100% in Chs and 84% in Ch without clinically significant late toxicity. These favorable results have been confirmed in more recent literature [50] where hyper fractionated high doses up to 81 Gy were used obtaining 5-year and 10-year survival rates for these patients of 73% and 44%, respectively. Fractionated Stereotactic Radiation Therapy (FSRT) with dynamic conformal arcs and intensity-modulated radiation therapy boost was used in the report of Bugoci et al. [51]. Even though the number of patients treated was limited (12 patients), the authors reported that in their experience FSRT as postoperative treatment of skull base chordomas resulted in promising overall survival results (76.4% at 5 years) , comparable with the published literature of particle therapy without significant complications but with only 37.5% of patients free of progression.

A. Stereotactic radio surgery - SRS

SRT can be delivered with different treatment systems: with classic Linear Accelerators (LINACs) using multiple beams focused on the target from different angles in an isocentric way; with multiple cobalt sources (Gamma Knife(GK), *Elekta Instruments AB, Stockholm, Sweden* or with commercially available dedicated machines, such as Cyber Knife (CK), *Accuray, Sunnyvale, CA, USA* a small LINAC mounted on a 6 degree of freedom robotic arm. These methods of irradiation are particularly useful for diseases with a limited postoperative residual volume, usually less than three cms. in diameter [52].

The North American Gamma Knife Consortium published a review of six institutions treating base of skull CH with Gamma Knife

radio surgery as the primary, adjuvant, or salvage management [53]. With a median follow-up of 5 years, of the 71 patients treated, 23 had died of tumor progression [54]. Overall survival at 5 years was 93% for patients who had not received prior radiation therapy and 43% for those who had received prior therapy.

Recurrent tumors can be controlled with gamma knife radio surgery mainly in case of residual lesions localized and small after initial aggressive resection [55].

The use of Cyber Knife for stereotactic treatment has introduced a new treatment technique used with typically fractionated regimens (1–5 fractions) that facilitate treatment of larger tumors with high doses per fraction [56]. As expected, patients with previous radiation therapy are at a higher risk of complications and poorer tumor control. In 18 patients treated with a median follow-up of 65 months, the local control was 59% and overall survival was 74%, with a disease-specific survival of 88.9% [57].

A comprehensive radiotherapy approach

Additional data are required to further delineate the role of advanced photon techniques is-a` -vis with PT that is actually considered the most appropriate irradiation technique in these tumors. The optimal radiation technique for a patient depends largely on the extent of surgery, the biological profile, the experience of the professional team, and the availability of resources. The published data are difficult to compare because of their retrospective nature and the length of their follow-up.

Many clinical series with patients postoperatively treated with several irradiation methods found that the type of radiation seemed not clearly influence recurrence rate, however these studies were usually small, retrospective, made in a very long life span and very heterogeneous with different selection bias [62,63].

In a meta-analysis of recent studies Di Maio et al. (64), found that 5-year PFS and OS were 50.8% and 78.4%, respectively, and no significant differences in 5-year OS were observed among photon radiotherapy, gamma knife surgery, PBT, and CIRT, but 5-year PFS was lower in gamma-knife surgery. Although doses of photons delivered were lower than those of protons and carbon ions, these results suggest that Chordoma may possibly be controlled when a sufficient dose is delivered in well selected cases, regardless of the radiation quality. Advanced treatment planning technologies are able to compensate for the less favorable dose distribution traditionally achieved with conventional EBRT techniques. It is to note that Chs require less high-level doses and can be treated more easily and successfully.

Further progress both in photon and particle radiotherapy is definitely required to improve the results in these radio resistant and invasive tumors that develop at a very complicated location. Although PT continues to be recommended as the radiation technique of choice, considering also the restriction for referral to the relatively few existing centers, other irradiation modalities may have a role in selected patients. PT could result particularly useful in tumors large and with complex shape that encompass an area too large for SRS, and achieve a high enough dose with generally acceptable toxicity that is not otherwise achievable with EBRT. Collectively, at present, the treatment modality should be selected on the basis of not only the tumor location, size, and shape but also the experiences of each institute.

Systemic therapy

Chemotherapy (CHT) has demonstrated to be largely ineffective for these slow-growing tumors and studies reporting the use of cytotoxic agents have not demonstrated clinically significant activity [6,65-67]. Different drugs have been tested with poor results and the evidence on treatment from literature mainly refers to anecdotal reports and at present, no drugs are approved for the treatment of advanced Chand overall, no evidence is available to recommend CHT. Published series regarding CHT of Chand Chsare scarce and most of these only give few details about primary histology, agents and regimens used, making impossible to define a standard CHT approach. Most chemotherapeutic regimens are currently considered in locally advanced or metastatic disease in a palliative setting often after several recurrences in patients not treatable with any other approach [68].

Molecular target-drugs, anti-PDGFRBimatinibmesylate has shown a certain activity in Ch, as detected in a prospective Phase 2 study and reported in several observational retrospective series [69-71]. Recently, there has been a renowned interest in exploring molecular therapy for Ch, as these tumors appear to have tyrosine kinase and related pathway mutations [72].

Limited data are available about the role of CHT in patients with advanced Chondrosarcoma: conventional CHT has very limited efficacy, the highest benefit being observed in mesenchymal and dedifferentiated Chs [73].

The characterization of molecular pathways involved in the oncogenesis of Ch and Chsand preclinical studies are needed to design clinical trials and classify targets that could be used in order to improve the prognosis of patients with advanced disease.

Conclusion

Ch and Chs are rare, slow-growing, locally aggressive neoplasms that in about one third of cases occur at the base of the skull near the spheno-occipital area. These tumors are challenging to treat due to their complex shape and proximity to very critical structures. Surgery continues to be the first choice of treatment and the primary modality in their management. Radiation therapy is often recommended regardless of resection status. The optimal treatment strategy includes surgicaldebulking, followed by irradiation. Radiation techniques able to cover the target with adequate doses and to reduce the risk of treatment are evolving. Particles (protons and carbon ions are more and more used and are considered a standard of irradiation but their wider use deserves further study in comparison with modern photon-based radiotherapy techniques. Proton-beam therapy with wide en-bloc excision is the accepted treatment standard in the management of chordomas at many quaternary-care cancer centers. No role at the moment is advisable for systemic therapies.

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