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A Review of Current Radiation Therapies for the Treatment of Metastatic Brain Tumors

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Abstract

The treatment of brain tumors has evolved over the past few decades. While whole brain radiation therapy was the standard of care in the management of tumors for years, stereotactic radiation has for the most part replaced the technique in the management of metastatic tumors of the brain. In this review, the current indications are reviewed for both whole brain and stereotactic radiation therapy in the management of metastatic cancers involving the central nervous system, the most common types of malignancies diagnosed in the brain.

Keywords: radiosurgery, whole brain radiation, prophylactic cranial radiation, history of cranial radiation

1. Introduction

The incidence of metastatic cancer involving the CNS is increasing and was >220,000 cases in the US alone in 2015, >20 times the incidence of high grade glioblastoma (GBM) [1, 2]. The four most common tumor types that metastasized to the brain were *lung > breast > melanoma > renal cell*—1,2,3,4, with median survival worse than those reported for primary CNS malignancies—8 *vs.* 13 months for GBM [1–4].

This increase in CNS involvement may be associated with the increased survival associated with improved therapy for the primary sites, permitting micrometastases in the CNS to become apparent. The management of CNS metastases remains ineffective [1, 2]. Thus, ‘subjects are living longer with cancer’, but also, and perhaps as a consequence, have an increased risk of developing metastases involving the CNS—a ‘safe haven’ from systemic chemotherapy [4].

The incidence of intracranial metastases observed at the times of autopsy was reported half a century ago and revealed that 5% of subjects with all types of cancer possessed brain metastases [5]. In the 1950s, the diagnosis of cancer involving the brain was made from clinical symptoms such as headaches, confusion, seizures, etc. and confirmed by physical findings such as papilledema hemiplegia, ataxia and aphasia. Further evidence could be obtained by electroencephalograms (EEG) and later carotid angiography and nuclear brain scanning were used [5]. With the advent of 'computerized axial tomography' (CT) and 'magnetic resonance imaging' (MRI), more exact delineation of the degrees of brain involvement is now possible, and higher incidences of metastatic brain disease are now appreciated [2, 4].

2. Radiation therapy

Radiation therapy (RT) has been the mainstay in the management of CNS metastases. Since the presentation is often multi-focal, surgery is not indicated [4]. However, responses of tumor metastases to whole brain radiation therapy (WBRT) (the current standard of care) are usually incomplete and of short duration and often accompanied by local toxicities, such as neurocognitive loss, etc. [4].

Whole brain radiation therapy (WBRT) was the treatment of choice in the past [6]. WBRT was usually started with a warm up dose of 50 cGy on the first treatment day increasing gradually to 200 cGy over several daily fractions to a planned total dose of 3000–4000 cGy [6].

The advent of glucocorticoid steroids controlled the radiation side effects such as headaches, papilledema, etc. and allowed higher daily doses of radiation to be given without exacerbation of intracranial edema, etc. [7, 8]. Although palliative care was provided, neurocognitive and other neurological/behavioral disorders still existed [9]. Also, the doses of WBRT administered were insufficient to treat subclinical metastatic disease that is not seen on the imaging tools available. The common dose schedules used were 3000 cGy in 10 fractions or 4000 cGy in 16 fractions [6].

With improved knowledge regarding tumor biology and more comprehensive tumor registries, certain tumors were found to have a higher propensity for brain metastasis—*lung > breast > melanoma > renal cell*—1,2,3,4 [4]. In subjects with these types of tumors prone to brain metastases, prophylactic brain radiation at lower doses began to be included in subject care plans. The goals have always been to kill off microscopic involvement, improve disease free survival with improved quality of life (QOL) and diminish morbidities associated with brain metastases.

2.1. Radiosurgical devices

With the development of radiosurgical instruments such as the Gamma Knife and Cyber Knife, it is possible to radiate individual metastatic lesions with great accuracy. In combination with MRI techniques, stereotactic radiosurgery (SRS) has become the most widely used procedure to reduce metastatic CNS cancer lesions and has also reduced the incidence of radiation-associated neurocognitive effects [9–13]. The exact radiation dosing varies depending on the size and number of metastases [13, 14]. As these techniques have improved, combining

WBRT with SRS has been evaluated, and after multiple studies, no increase in overall survival (OS) (but an increase in local control) with WBRT after surgery/radiosurgery has been observed [15–18]. However, there still remains scenarios in which WBRT may be beneficial. Later in the chapter, we will review this evidence for the use of WBRT.

3. Adjuvant or prophylactic cranial irradiation (PCI)

3.1. History and rationale

The recognition that certain cancer cell types have a propensity to spread to the central nervous system created interest in adjuvant or prophylactic cranial irradiation (PCI) for some malignancies at lower therapeutic doses [7, 18, 19].

3.2. Childhood leukemia: PCI

In children with acute leukemia, it was recognized that the CNS is a sanctuary site for malignant cells and PCI became the standard therapy for many years [19–22]. However, because of the neurocognitive/behavioral defects and the decrease in IQs that were noted in children who received PCI for childhood leukemia, other treatment methodologies were compared with and without radiation [20]. In 2003, a meta-analysis of 43 randomized trials concluded that radiotherapy can be replaced by long-term intrathecal therapy and a 2009 prospective randomized trial confirmed with 501 subjects confirmed that radiation can be omitted from treatment [21, 22]. As such, PCI in the setting of leukemia is not routinely used in clinical practice.

3.3. Small cell lung cancer: PCI

Small cell carcinoma of the lung (SCLC) has a propensity to metastasize to the brain and CNS, where there has been great enthusiasm for the use of PCI. NCCN guidelines still support its use [7, 8, 23, 24]. However, due to the associated neurodegeneration, there is a trend to only treat the brain with radiation, if lesions are detected [23]. The original rationale for prophylactic cranial irradiation (PCI) in limited small cell cancer that was advocated by Hansen in 1973 is that CNS relapse in small cell lung cancer is analogous to isolated CNS relapse in Acute lymphoblastic leukemia (ALL) [7].

The first meta-analysis published by Prophylactic Cranial Irradiation Overview Collaborative Group supporting the use of PCI in limited SCLC was published in 1999 and proved that PCI reduced the incidence of brain metastases by 50% with an absolute survival advantage of 5%. This 5% was the same amount of absolute survival advantage seen with thoracic radiation after induction chemotherapy in limited SCLC [25].

Of importance, a high proportion of subjects with SCLC had specific cognitive defects prior to PCI without any significant deterioration following PCI. For extensive SCLC, the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Group showed a slight improvement in survival with the addition of PCI after induction therapy, but in absolute terms, the benefit was minimal after 1 year; survival in the radiated group was 27.1%, as

compared with 13.3% in the control group. In the PCI group, two subjects remained alive at 24 months, while in the control (no PCI), all subjects were dead by 18 months [24].

NCCN treatment guidelines continue to recommend PCI for SCLC, even though there have been significant advances in the imaging and treatment of brain metastases. Since many of the original studies advocating the use of PCI were published using CT as the imaging choice for the brain, it is now postulated that many small brain metastases that were missed by CT would have been detected by sensitive MRI [8]. The fact that MRI scanning detects SCLC metastasis 24% of the time, as opposed to 11% with CT, means that there will be fewer patients with undetected cranial metastases after imaging with a contrast-enhanced MRI study, thus possibly reducing the role for WBRT going forward.

There is also a greater awareness of the potential deleterious effects of whole brain irradiation on stem cell and immune modulating cell compartments within the brain, the importance of which in humans was originally reported in 1998 [25]. This observation encouraged the development of techniques to limit radiation dose to critical structures such as the hippocampus and sub-ventricular zone [26–28]. Currently, a Phase 3 trial—NRG-CC003: A Randomized Phase II/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer—is comparing partial cranial radiation with and without sparing of the hippocampus in subjects with small cell lung cancer (SCLC) involving the brain, will be completed by 2019 [26].

As such, the guidelines for PCI in limited SCLC may change within the next few years. Since there is improvement in survival with PCI, the benefits and risks should be discussed with each subject to allow them to determine if they want the therapy.

3.4. Non-small cell lung cancer (NSCLC): PCI

NSCLC is the most common cancer to metastasize to the brain and 7.4% of subjects with NSCLC have brain metastases at presentation of primary disease [4]. Another 25–30% of the subjects with NSCLC will develop brain metastases during the course of their disease [2, 27]. Because of the improvement in absolute survival seen in limited SCLC, the radiation therapy oncology group (RTOG) has performed two trials of prophylactic cranial radiation in NSCLC cancer.

The first RTOG trial study population included 161 subjects treated for medically or surgically inoperable primary cancers and 26 subjects undergoing adjuvant postoperative mediastinal irradiation following attempted curative resection of primary cancers found to have metastasized to hilar or mediastinal lymph nodes [28]. Published in 1991, the 94 subjects randomized to chest irradiation alone had a 19% incidence of brain metastases. In subjects randomized to receive prophylactic cranial irradiation, there was a 9% incidence of brain metastases. Despite the dramatic improvement in local control of brain disease, no survival difference was observed between the treatment arms. Because of the absence of reliable therapy for the primary disease at that time and the lack of effective systemic therapy to prevent dissemination to extra-thoracic sites, prophylactic cranial irradiation for inoperable NSCLC was not justified in routine clinical practice [28].

A more recent RTOG study evaluating PCI in NSCLC was published in 2011 [29]. RTOG 0214 was performed with subjects that had locally advanced NSCLC. Subject eligibility was Stage III NSCLC without disease progression after treatment with surgery and/or radiation therapy

(RT) with or without chemotherapy. This study showed a decrease in brain metastases in the PCI group [7.7% (PCI cohort) at 1 year *vs.* 18.0% (observation) at 1 year]. However, there was no effects on survival due to the devastating effects of systemic NSCLC without effective systemic therapy. The disease free survival and overall survival were essentially the same (1 year OS 75.6 *vs.* 76.9%; DFS 56.4 *vs.* 51.2%) [29].

In another study, Sun *et al.* reviewed the neuropsychiatric profiles for these subjects and showed that, although PCI did not significantly impact overall reported quality of life PCI in Stage III NSCLC, did not reduce global cognitive function or quality of life (QOL), and there was a significant decline in memory at 1 year in the PCI group [30]. Given that there is no survival benefit from PCI in NSCLC and that there is cognitive toxicity, at the present time, PCI is not recommended by the NCCN for NSCLC [31].

4. Metastatic brain carcinoma

Historically, the treatment of metastatic brain disease was whole brain radiation ranging in doses of 2000 cGy in 5 fractions to 4000 cGy in 16 fractions [3]. This resulted in good palliation and reduction of steroid dosage, but poor local control. Studies have shown an improvement in symptoms in 64–83% of subjects after treatment with WBRT alone and have also demonstrated an increase in median overall survival (OS) from 1 month with no treatment to 3–7 months following WBRT [32]. When reviewing data contained within studies of metastatic brain disease in the RTOG, control of disease is accomplished in approximately 50% of subjects at 6 months [32].

The development of radiosurgical techniques for brain lesions paralleled the studies of metastatic cancer involving brain conducted by the RTOG [32]. In 1987, the first report study of 12 patients who were treated with radiosurgery using a linear accelerator for brain metastases with a dose of at least 2000 cGy was presented [33].

With the advent of CT and MRI neuroradiologic imaging, the computer revolution allowed better planning of treatments and radiosurgery began to be used in earnest for treatment of brain metastases because of the knowledge that whole brain radiation had a failure rate of about 60% [2–4].

Many studies have been reported for SRS and RTOG recursive partitioning analysis (RPA) that was derived from studies of whole brain radiation and the use of radiation sensitizers [33]. This platform analysis has allowed a better appreciation of results [33].

Recursive partitioning analysis (RPA) and statistical analysis has created a regression tree according to prognostic significance. Eighteen pretreatment characteristics and three treatment-related variables were analyzed. The RPA tree is based on four parameters (age, Karnofsky performance status (KPS), presence or absence of extracranial metastases and the control status of the primary tumor). The best survival (median: 7.1 months) was observed in subjects < 65 years of age with a Karnofsky Performance Status (KPS) of at least 70 and a controlled primary tumor with the brain the only site of metastases. The worst survival (median: 2.3 months) was seen in subjects with a KPS < 70. The following three classes are delineated: Class 1: subjects with KPS ≥ 70, <65 years of age with controlled primary and no extra cranial

metastases; Class 2: KPS < 70; Class 3: all other subjects who were not 1 or 3. Using these classes or stages, new treatment techniques can be tested on homogeneous subject groups.

The important point regarding RPA is that if subjects are randomized in the same RPA class group two treatments can be compared without worry that differences in survival were due to subject selection. Numerous studies have been published in the field of radiosurgery for brain metastases, and it is beyond the scope of this chapter to provide a detailed analysis.

A decision platform from ‘Intracranial Stereotactic Radiosurgery’ shows appropriate management for patients with 1 and 2–4 brain metastasis in 2016 (Figure 1) [32, 33].

Chart 1

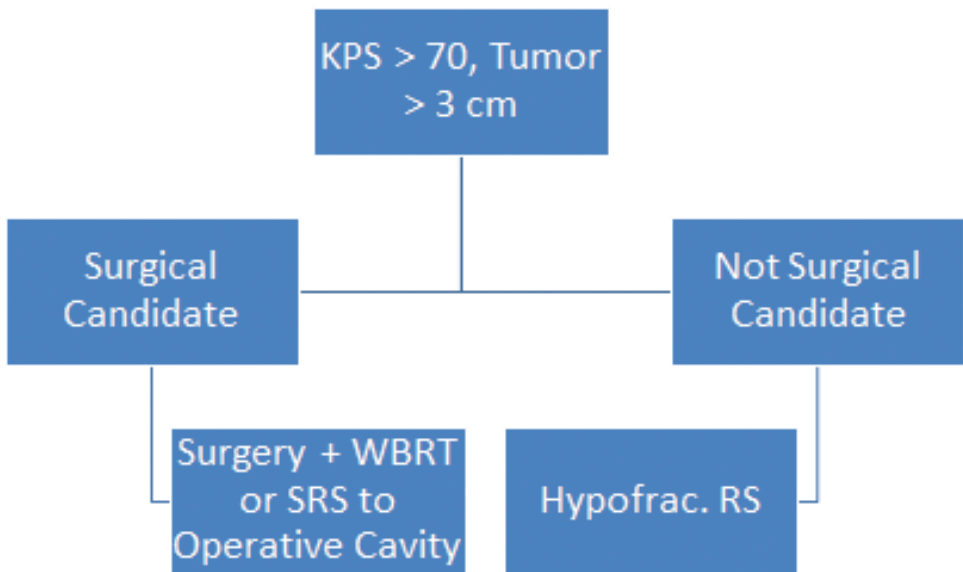
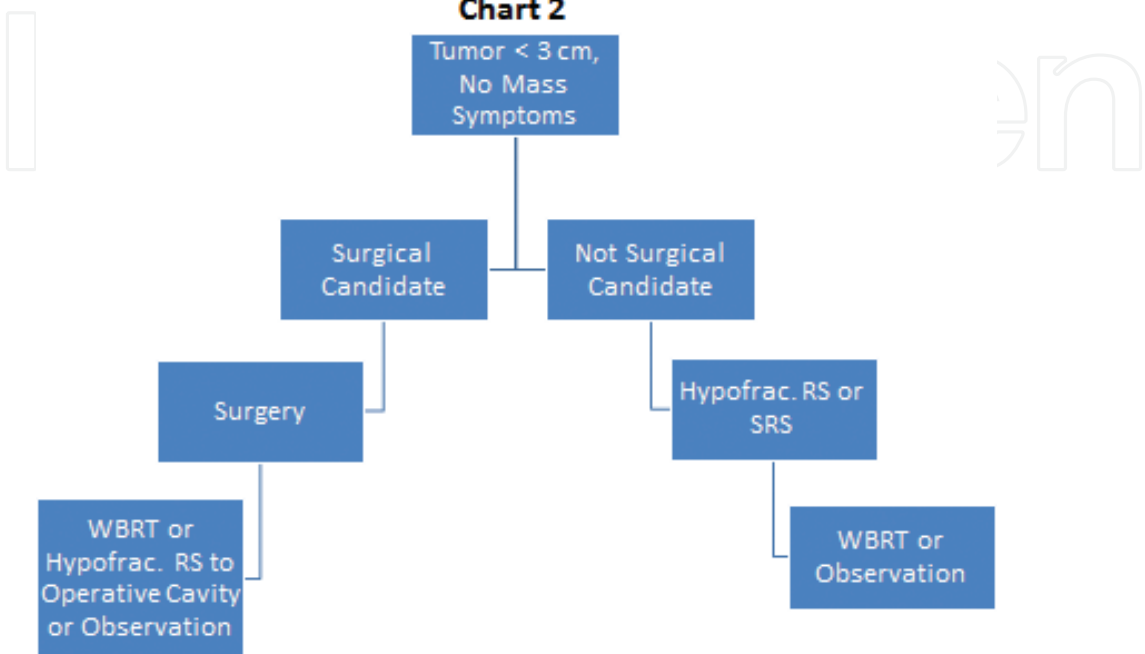


Chart 2



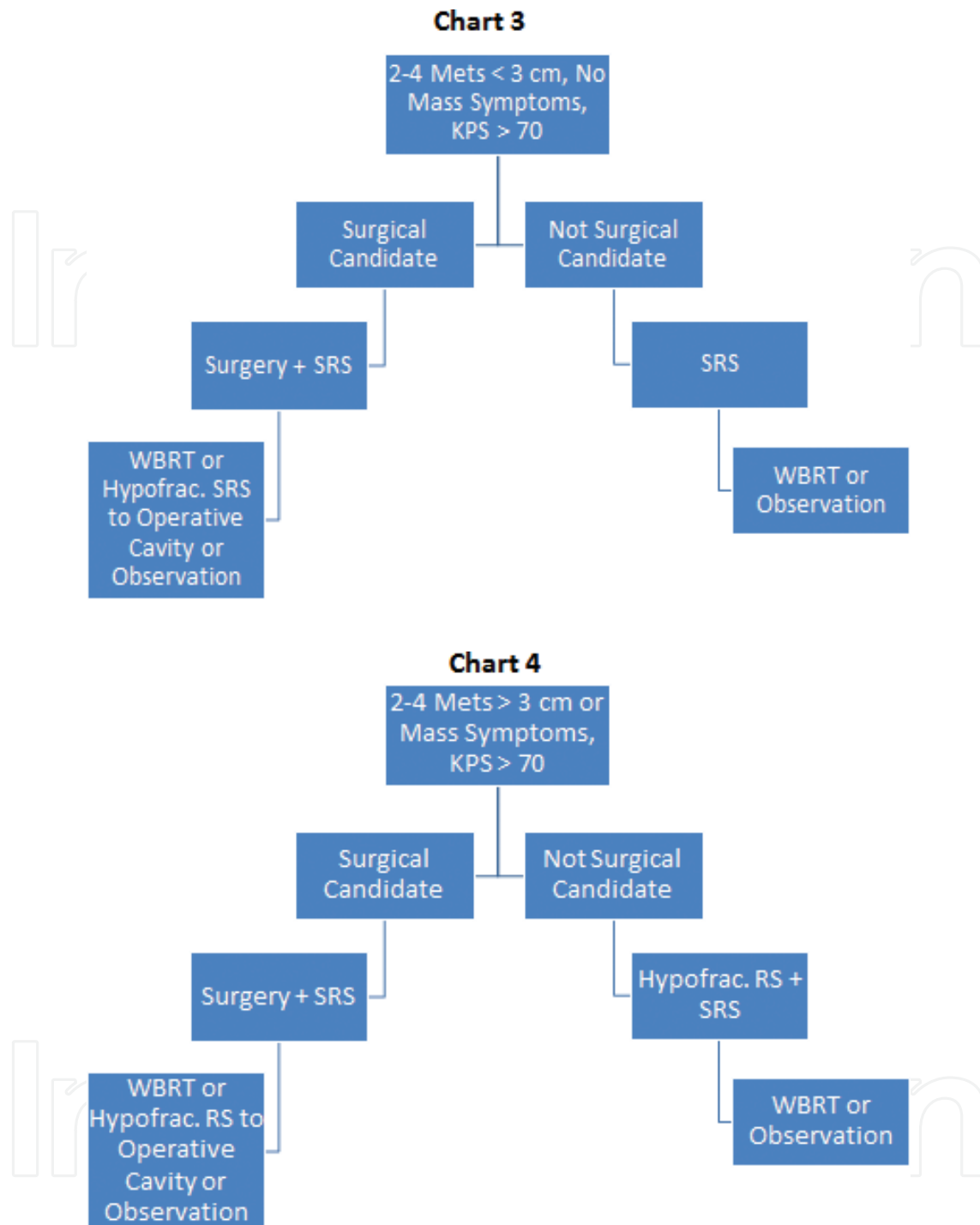


Figure 1. Flow chart for treatment of metastatic brain lesions.

Patients that have ≥ 5 metastatic lesions involving the brain have not been studied in any randomized trials. This is unfortunate because survival has varied considerably due to subject selection [33]. There is one randomized study group in Japan, which was a multi-institutional prospective study that included 1194 patients (76% with lung cancer). The aim was to examine whether survival after SRS without WBRT as initial treatment for subjects with 5–10 brain metastases (median 6) was inferior to that of patients with 2–4 lesions. Size limits were metastases < 3 cm in longest diameter, largest tumor < 10 ml in volume and total cumulative volume ≤ 15 ml. Median

survival was longest in subjects with one lesion ($n = 455$, 13.9 months). However, subjects with 2–4 lesions had comparable survival to subjects with 5–10 lesions (median survival 10.8 months, hazard ratio 0.97, 95% confidence interval 0.81–1.18). This met the pre-specified definition of non-inferiority, despite the development of new lesions in >60% of subjects. Further salvage SRS was done in more than 40%, and 9% received salvage WBRT. The delivery of further SRS or WBRT was not significantly different between the groups. Grade 3–4 adverse events occurred in up to 3% of subjects in each group; only 8% of subjects died from their brain disease [34].

5. Conclusion

Radiation therapy remains a secondary therapy when surgery is not an option.

Several facts have emerged. Local control of brain metastases does not translate into increased survival, although there may be long-term survivors in the RTOG RPA Class 1. Stereotactic radiosurgery with or without whole brain radiation is appropriate in the treatment of patients with 1–3 metastasis. Whole brain radiation when combined with SRS may have long-term deleterious effects on neuro-cognition. In combination with the newer immunomodulators, WBRT and/or SRS therapy may improve the usefulness of radiation [35].

The main three questions that remain to be answered regarding the treatment of metastatic brain disease focus on avoidance of toxicity from brain radiation through tissue sparing and dose reduction.

Can hippocampal sparing help avoid neurocognitive deficits? Will the development of novel radiosensitizers allow the use of lower doses of radiation and still achieve strong immune modulation? Can more sensitive MRI better define the extent of cancer metastases in the CNS and obviate the need for whole brain radiation in SCLC and ALL subjects.

All good questions to be answered in future randomized clinical trials with WBRT *vs.* SRS.

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