A New Frontier in Fighting Brain Cancer: Cutting Edge Magnetic Resonance Imaging Techniques

ABSTRACT

Of the currently available brain imaging techniques for diagnosing tumors, diffusion-weighted MRI and perfusion MRI are cutting-edge techniques and may provide improved diagnostic capacity compared to traditional techniques such as positron emission tomography. Moreover, they are fully non-invasive and avoid the exposure to radiation. While MRI in general has been used in research and medicine for decades, the more recent development of multi-modal and multiparametric imaging in neuro oncology holds much promise for the enhancement of diagnosis, prognosis, and patient-tailored treatments in this field. This review will evaluate how these various imaging techniques provide clinical value above and beyond previous techniques.

Introduction

Neuro-oncologists are increasingly using diffusion-weighted imaging (DWI) and perfusion MRI to not only diagnose brain tumors, but also guide surgical procedures and monitor the tumor treatment response. DWI allows for the detection of water diffusion. Water diffusion is inversely related to tumor cellularity- meaning the increase of one causes the decrease of the other; in other words, as cellularity decreases due to damage or altered structure, the free diffusion of water in a tissue increases, allowing for the noninvasive detection of tumor cellularity Perfusion MRI techniques also help oncologists evaluate tumor structure by analyzing tumor vascularity in the context of neoangiogenesis, a process where new blood vessels grow to support the invasion of tumor cells. These advanced techniques are becoming the standard of use for the detection, characterization, and staging of viable tumor lesions. Additionally, these tools become especially useful in malignant tumors such as glioblastomas, metastatic tumors, and lymphomas.

Within DWI and perfusion MRI, different novel MRI analytic techniques further provide unique benefits to oncologists. For example, intravoxel incoherent motion (IVIM), found in DWI, is utilized, with the absence of contrast agents, for the evaluation of tissue perfusion and separation of microcirculation from true water molecular diffusion.[1] Diffusion kurtosis imaging (DKI) can serve a multitude of tasks.[2] DKI locates non-Gaussian diffusion, which may help describe the brain regions' structural components.[2] Perfusion MRI comprises three main methods that are all primarily used to evaluate malignant brain tumors.[3] The three primary perfusion MRI techniques used in neuro oncology—dynamic susceptibility contrast (DSC) perfusion MRI, dynamic contrast-enhanced (DCE) perfusion MRI, and arterial spin labeling (ASL)—gift unique characterizations of the pathophysiology of a patient’s pre- and post-treatment brain tumors.[4]

As a biomarker of the glioma outcome, the tumor microvessel area (MVA) could be accurately derived from the relative cerebral blood volume (rCBV) calculated from the DSC perfusion MRI.[5] DCE perfusion MRI differentiates mature from immature tumor vessels.[6] ASL can be used to obtain cerebral blood flow (CBF), which is extremely useful for oncologists because CBF may predict tumor vascular normalization, a therapeutic strategy aimed towards preventing angiogenesis.[7] Cerebral blood flow (CBF) is the rate at which the arterial blood is transported into the brain’s capillary bed. Contrast-enhanced susceptibility-weighted imaging (CE-SWI) may further evaluate the cellular and vascular consistency of tumors above and beyond the ability of techniques without contrast agents.[8] This review will discuss each advanced MR imaging techniques separately—diving deep into the clinical usefulness as well as limitations of each method.

Discussion

Apparent Diffusion Coefficient Characterizes Many Tumor Aspects and Tracks Antiangiogenic Drugs Response

Diffusion-weighted MRI is able to detect the magnitude of this microscopic, subvoxel water motion and this is used to derive several metrics, including the apparent diffusion coefficient (ADC), a measure of the degree of water diffusion within a voxel.[9] Water molecules found in extracellular, intracellular, and intravascular regions are restricted in their movement differently, producing differential ADC signals and allowing for tissue-type segmentation[10] Specifically, each space is characterized by different microscopic anatomical barriers, which leads to differential perfusion of water, both in terms of the directionality and extent of diffusion.[10] Generally, ADC gives oncologists a fair approximation of the water diffusion within the extracellular and extravascular space.[11] Since tumors are composed of tightly packed cells (they are highly cellular), the extracellular water motion within this tissue is restricted. So when the tumor cellularity is increased, the water diffusion is decreased, which means the ADC is also decreased.[11] Generally, necrosis or cellular lysis, caused by antitumor treatments, can decrease cellularity.[12] Because decreased tumor cell population precedes any measurable tumor size change, DWI can thus predict early treatment outcomes, monitor early treatment response, and detect recurrent tumors.[13]

Shifts in the ADC symbolizes certain long-term patient responses to treatments.[26] For example, the degree of change in ADC after chemotherapy is predictive of patient's overall survival.[27] Changes in ADC might also help identify chemotherapy-resistant tumor types.[27] Therefore, ADC is a valuable tool in monitoring the patients' treatment response.[27] However, when oncologists analyze pretreatment ADC in recurrent glioblastomas, they found that ADC is effective in predicting antiangiogenic therapy's response, but not chemotherapy's response.[28] Therefore, monitoring ADC over the course of treatment serves as a tracker for prescription of antiangiogenic therapy in recurrent glioblastoma but perhaps not when utilizing chemotherapy alone.[28]

Apparent Diffusion Coefficient's Inaccurate Representation of Tumor Cellularity

However, this technique is not without limitation. Since ADC is affected by capillaries' microcirculation, it may be susceptible to changes in vascularization.[22] Malignant brain tumors express higher tumor cellularity and vascularity compared to benign brain tumors.[23] Unlike the high tumor vascularity, which increases ADC, high tumor cellularity decreases it.[24] This phenomenon proves that the DWI signal attenuation in hypervascular brain tumors can be influenced by two opposing manners, which, as mentioned previously, limits the ADC value for grading hypervascular brain tumors.[25] This under-performance can give rise to contradictory results. To account for this, tumor vascularity can be assessed through a pathology review of tumor sections.[22]

Moreover, different tumor subtypes may interfere with the use of ADC. High-grade gliomas, which are more invasive and harder to treat compared to low-grade gliomas, are heterogeneous regarding their microstructure and genetics.[15] High DWI signals can result from tumor coagulation necrosis or ischemia.[16] However, highly cellular tumor areas in combo with inflammatory processes can dramatically restrict the intensity of the diffusion signal, adding complexity to the characterization of tumor progression.[16] As a result, the usage of mean ADC values to accurately grade tumors can be ineffective due to this heterogeneity;[17] for instance, tumor necrosis can restrict water diffusion and falsely suggest high cellularity; indeed, tumor cell density, metabolic activity, ischemia, and compression are all possible factors responsible for the restriction of diffusion within and around cancerous tissue.[20]

Intravoxel Incoherent Motion to Differentiate Perfusion from Diffusion

A pseudo diffusion, often observed in abnormally oriented capillary blood flow, can interfere with diffusion measures in DWI images. This occurs only when the *beta* parameter of a DW image are set to relatively small values.[29] To distinguish true diffusion from pseudo diffusion, we can identify the isotropic diffusion in water from the "incoherent motion" present in blood vessels.[30,31] This can be done by taking multiple DWI images while systematically altering their b values corresponding to the weighting of diffusion (where higher b values result in higher-intensity images given a constant degree of diffusion). For each voxel, the b value used across multiple images and the resulting intensity of the voxel can be fit to previously-defined models which differentiate free water diffusion from that observed in blood.

Multiple forms of these models have been employed. Mono-exponential fitting involves the use of a single variable while bi-exponential fitting involves the use of multiple variables. In recent research, scientists, using simple mono-exponential fitting, which doesn't account for the contribution of the perfusion effect, discovered that

lymphoma patients have drastically lower ADC compared to other tumor patient groups.[40] Meanwhile, scientists, using the bi-exponential fitting, which accounts for the contribution of the perfusion effect, discovered that lymphoma patients have similar "true" diffusion parameters compared to other tumor patient groups.[40] This finding suggests that the ADC difference is strongly correlated to the perfusion effect's contribution and perfusion of blood may sometimes produce spurious differences between groups when not taken into account.[41] It can therefore be concluded that a mono exponentially fitted ADC may not give oncologists the best accuracy in terms of the inverse correlation between the ADC and tumor cellularity.[42,43]

However, IVIM also has its limitations. For example, it requires a high signal-to-noise ratio, when oncologists use it to separate perfusion from diffusion.[36] Furthermore, the phenomena of vascular tubular flow and glandular secretion can produce artifacts.[37] Lastly, different vessel sizes can produce different IVIM signals and result in different levels of sensitivity.[37] All of these challenges makes the differentiation process that much more difficult and future efforts should address these remaining limitations.

Diffusion Kurtosis Imaging Reflects Gray and White Matter's Structural Components

The Gaussian law can be easily observed in free, unobstructed, diffusion.[44] Unsurprisingly, a non-Gaussian distribution occurs when the diffusion of water molecules are restrictively affected by the complex microstructure of different tissue types.[44] Therefore, the tissue's microstructure, namely the cell membranes, organelles, and water compartments, could give rise to specific non-Gaussian diffusion patterns.[44]

DKI is a modified version of DTI. Compared to diffusion tensor imaging (DTI), non-Gaussian diffusion, derived from diffusion kurtosis imaging (DKI), can more accurately evaluate aspects of both normal and pathologic tissue by taking advantage of this property.[45] The microstructural complexity index might thus be represented by the mean kurtosis (mk).[46] Since MK works regardless of whether the tissue is spatially oriented in a certain plain, it proves to be a better venue compared to DTI-derived fractional anisotropy (FA) in the context of neurooncology.[46] For instance, MK can be applied for both the gray and white matter without regard to the directionality of the underlying healthy cytoarchitecture.

Diffusion Kurtosis Imaging Reliably Grades Glioma

Increased kurtosis is indicative of increased tissue complexity in high-grade glioma.[47] A variety of events such as hemorrhage, tumor invasion, necrosis, endothelial proliferation and more, could be involved in increasing the tissue complexity of tumors.[47] Unsurprisingly, decreased kurtosis parameters are indicative of decreased tissue complexity. This may be used to detect low-grade glioma, which have more homogeneous and less packed cells.[47] Studies have pinpointed that the difference between the intra- and extracellular space can be used to identify low-grade from high-grade gliomas.[48] This difference might be attributed to the different characteristics between these forms of gliomas.[49] High-grade gliomas have more crowding cells and myelin breakdown products, which makes the membrane structure tightly packed.[49] Low-grade gliomas have more differentiated, neoplastic astrocytes, which makes the membrane structure loosely packed.[49] Thus, while both high-grade and low-grade gliomas have more kurtosis than normal tissue, differential kurtosis within tumor tissue may provide clues to which subtype best characterizes a tumor in the absence of a biopsy.

Dynamic susceptibility contrast perfusion MRI can measure CBV

Dynamic susceptibility contrast (DSC) perfusion MRI operates similarly to the popular T2*-weighted MR techniques (e.g., ASL, discussed below) that are often used for the estimation of rCBV in functional MRI.[55,56] However, DSC perfusion MRI instead uses gadolinium-based contrast agents in order to increase signal to noise ratio. This is useful because rCBV can be used to predict tumor vascular morphometry, such as MVA (discussed below).[57] However, it should be noted that rCBV can't accurately predict such measures when the glioblastomas have heterogeneous vessel sizes, which is often the case.

One major problem to consider is contrast agent leakage, which often occurs in tumor vessels when the blood-brain barrier is severely sabotaged.[58] This can amplify the abnormal effects on T1 or T2*.[59] The effects T2* exerted as a

consequence of contrast-agent leakage can be influenced by the tumor cells' density and spatial distribution.[59] Moreover, these effects could result in the addition of a susceptibility calibration factor, which could partly, but not fully, compensate for the leakage effects.[59] Due to these limitations of T2, T1 kinetic parameters are more reliable when it comes to analyzing complex tumor vessels with mostly heterogeneous vascular characteristics as these tumors are more likely to present with blood-brain barrier damage.[60]

DSC Perfusion MRI Eliminates the Problem of Pseudoprogression

After glioblastomas patients were treated with chemoradiotherapy, oncologists took into account the presence of transiently enlarging, contrast-enhanced lesions in order to decide whether to continue or switch to a second-line therapy.[61] Pseudoprogression is the detected expansion of a tumor that is not caused by the tumor's actual growth. In other words, it's false tumor growth. It occurs because during immunotherapy, immune cells surround the tumor and enlarge the region. Inaccurate interpretation of the pseudoprogression in tumors have reduced salvage treatment trials.[62] To prevent the false-positive evaluation of a new drug's effects, it is therefore necessary to exclude pseudoprogression.[63] Oncologists often rely on the histopathologic diagnosis, which is derived from second-look surgery and highly prone to sampling errors, to separate the early tumor progression cases from the pseudoprogression ones.[64] To limit these sampling errors, alternative methods have been integrated, namely the interpretation of MRI findings and clinical manifestations.[65] Dynamic susceptibility contrast perfusion MRI is a specific alternative that researchers have looked to.[66]

Previous studies show that we can predict the patient's chance of one-year survival based on how their rCBV percentage has changed following radiation-temozolomide therapy.[67] Scientists have developed a tool to differentiate pseudoprogression from true progression: a rCBV-derived parametric response map.[68] It was also found that true tumor progression can be expected if the patients experience a rCBV decrease three weeks after therapy.[69] After chemoradiotherapy, early tumor progression patients experience something the pseudoprogression patients did not: negative changes of skewness and kurtosis of rCBV histograms[70] (rCBV histograms shows the distribution of normalized rCBV values over time). In short, as vascular proliferation remains a prominent element indicative of true tumor progression, DSC perfusion MRI likely holds value in the detection of true tumor progression out of many pseudo progressions, despite its caveats.[72]

Microvessel Density/ Area

Compared to MVD (microvessel density), MVA (microvessel area) shows both the microvessels' density and character, which gives oncologists a better evaluation of the tumor's microvessel morphometric complexity, overall vascular surface area, and stages of angiogenesis.[51] For instance, an increase in MVD suggests a decrease in vessel size. There are many explanations for this phenomena such as the presence of delicate microvessels or glomeruloid vascular structure (made of tumor-derived immature microchannels) in invasive tumors in the brain's grey matter.[52] The field has thus turned to MVA as a better predictor for patient survival than MVD, which has less ability to predict tumor progression.[53] Specifically, in high MVA tumors, glomeruloid vessels are more common, while low MVA tumors possess more delicate (capillary-like) vessels.[53] Importantly, such high MVA tumors are more likely to undergo metastasis or invasion. This suggests that prognosing a glioma patient involves the examination of their tumor morphology and techniques such as MVA, which can do so without surgery, may non-invasively provide guidance for treatment options (e.g., the decision to surgically remove tumors).

Arterial Spin Labeling to Predict Tumor Normalization and Drug Response

As stated, tumor vascular characteristics can be indicative of certain therapeutic responses.[91] This is due, in part, to the fact that particular tumor vessels' patterns play a big role in increasing or decreasing the efficacy of chemotherapeutic drug delivery.[92] For instance, higher tumor blood perfusion is linked to more positive outcomes regarding antiangiogenic treatment.[93] Thus, high CBF, which may be assessed using arterial spin labeling (ASL), signifies low tumor vessels' permeability.[94] This makes the chemotherapeutic drug delivery to tumor cells more efficient and effective, giving a more favorable outcome.[95] Leveraging the endogenous tracer without any contrast agent injection, ASL noninvasively measures CBF[96] (An endogenous tracer is a molecule or subatomic particles that comes from within the system that are used to track another molecule. ASL's endogenous tracer is arterial blood

water protons tagged by a radio-frequency pulse prior to the blood entering the cerebrum). Aside from accurately evaluating the CBF, ASL is also valuable for assessing tumor blood-vessel attenuation and grading gliomas alongside other methods like MVA.[96] Due to all of its capability, ASL is highly helpful in cases where CBF is correlated to clinical outcome measures, such as in the context of drug delivery through the blood stream.[96]

Arterial Spin Labeling Depicts Efficacy of Drug Delivery

The structure and function of tumor vessels drastically change in angiogenesis.[97] By inhibiting vascular endothelial growth factor signaling, antiangiogenic treatment eradicates mutated vessels and reestablishes the normally-functioning vasculature.[98] This reestablishment of vasculature promotes effective drug delivery as it increases CBF and decreases tumor-induced hypoxia and interstitial fluid pressure, which may kill nearby cells.[99] So, increased tumor perfusion during chemotherapy might serve as a good signal of longer survival.[100] Cytotoxic chemotherapeutic agents showed different effectiveness in high-CBF patients versus low-CBF patients.[101] The high-CBF groups experience a longer median time-to-progression (TTP) compared to their negative-CBF counterparts.[102] High CBF can thus be used to predict favorable TTP and outcomes. Moreover, this is regardless of the MGMT promoter methylation status;[102] MGMT is an enzyme that helps tumors resist chemotherapy and its methylation-dependent expression thus impacts drug-treatment. In sum, high CBF demonstrates hyperperfusion and normalized tumor vessels, which may enhance drug delivery.[102]

Dynamic Contrast-Enhanced Perfusion MRI Detects Immature Vessels

While leakage of contrast agents may limit techniques like DSC, it may also be used to assess the vascular architecture of tumors[73]. Naturally, the intravascular compartment and the extravascular, extracellular compartment interchange contrast agents with each other at some rate.[74] To quantify the rate of this exchange, Dynamic Contrast-Enhanced (DCE) perfusion MRI uses a pharmacokinetic model, which can derive the transfer coefficient (Ktrans), which is indicative of the tumor's vessel permeability.[75] Brain tumors' contrast agents usually extravasates (leaks out from blood vessels) due to the presence of immature hyperpermeable vessels.[76] Measuring this extravasation is useful in two ways: differentiating mature tumor vessels from immature ones and identifying the tumor-vessel permeability[77]; both can be utilized as a biomarker for brain tumor progression.[77]

DCE perfusion MRI, in order to function, requires complex data acquisition and analysis that the DSC perfusion MRI does not.[78] First, determination of T1 values in brain tissue before contrast injection is required for the calculation of tissue contrast concentration curve with time.[79] After that, scientists need to accurately measure the arterial input function, which is the concentration of tracer (molecules with specific characteristics that allow them to trace a biological process) in the artery's blood.[80] This can be very challenging because inflow might disrupt either the MR signal intensity or absolute contrast concentration.[80]

Despite the required complexity, DCE MRI also has many advantages over other methods like DSC: three-dimensional acquisition of images, a higher signal-to-noise ratio, and a higher spatial resolution compared to DSC MRI.[81] Also, since DCE MRI can more sensitively monitor small vessels compared to DSC MRI, it could better track drug delivery.[81] In theory, DCE perfusion MRI also has other potentials such as the promise of developing more accurate pharmacokinetic models that can be used to modulate tumor drug delivery and patient's response to chemotherapeutic drugs based on estimates of tumor vascularity detected using other imaging techniques.[82] Ultimately, DCE perfusion MRI can be extremely helpful if used correctly and when its limitations are properly taken into account.[83]

DCE Perfusion MRI Improves Assessment of Patient's Drug Response

Oncologists also use dynamic contrast-enhanced perfusion MRI to evaluate the physiologic aspect of the regeneration of tumor vessels, namely the microcirculation.[84,85] Dynamic contrast-enhanced perfusion MRI is extremely useful because it can serve as a noninvasive tracker of not only tumor progression, but also treatment response.[86,87] Researchers have found that the combo method of DSC/DCE, MRI, and DWI performs better in differentiating recurrent glioblastoma from radiation necrosis compared to the combo the use of only MRI and DWI.[88] In other words, the addition of DSC or DCE improved diagnostic performance. Oncologists are encouraged

to include any form of perfusion MRI to their traditional MRI protocol of MRI and DWI, since perfusion MRI increases accuracy in the recognition of recurrent glioblastoma.[89] More importantly, the specific combination of conventional MRI, DWI, and DCE MRI (not DSC MRI) proves to have the best recurrent glioblastoma diagnostic performance.[90]

CE-SWI Highlights Tumor Necrosis and Vessels

Susceptibility-weighted images (SWI) are gradient echo sequences that are able to illustrate the cerebral veins and microhemorrhage.[103] SWI describes edema and contrast enhancement, examples of T2 effects related to T1 effects.[104] The capture of the tumor's architecture is necessary to evaluate tumor necrosis.[105] The tumor's architecture shown on SWI is much more useful compared to that shown on contrast-enhanced T1-weighted imaging because contrast-enhanced T1 imaging captures the tumor's architecture based on the presence of necrosis, cysts, and tumor boundaries, while SWI captures the tumor's architecture based on the presence of blood products and tumor vessels.[106,107]

When analyzing brain mass lesions using susceptibility signals, gadolinium-based contrast agents can be integrated into the procedure to improve the analysis.[108] SWI and contrast-enhanced (CE)-SWI can show similar susceptibility signals. But, there are cases when only the CE-SWI shows a particular susceptibility signal, meriting the use of contrast in some patients. Importantly, if oncologists use SWI before and after the contrast agent is applied, oncologists can more easily differentiate hemorrhages from veins.[109] This is because the signal intensity of blood vessels changes from the absence to presence of contrast agent while the signal intensity of hemorrhages, which take much longer to take on contrast agents, remains the same.[109] CE-SWI can be seen as a high-resolution, structural MRI, which has a great potential for contrast-enhancing tumor segmentation.[110]

Previous studies examining the effectiveness of CE-SWI have also shown that it can be used to detect tumor invasion zones.[111] These are zones that experience less tumor-cell density because tumor cells migrate away from these zones into the surrounding brain tissue for invasion.[112] Since this process can be fatal to patients, CE-SWI can be extremely helpful in detecting these processes. In pre-contrast SWI, susceptibility signals may detect highly pathological vessels, micro-hemorrhage, and extensive necrosis; however, CE is necessary for the detection of more subtle qualities such as tumor invasion zones.[113]

CE SWI Enhance Tumor Evaluation

SWI is a necessary addition to conventional imaging techniques because it contrasts and detects the tumor’s venous vasculature and hemorrhage, which could not be done using conventional imaging techniques.[114] By tracking the intratumoral susceptibility signal (ITSS), oncologists have used SWI to non-invasively grade primary brain tumors.[115] Tumor grading is a process of identifying the levels of malignancy of the tumor base on its characteristics. Glioblastomas are high-grade tumors that consist of hemorrhage and upregulated micro vascularity.[116] SWI is valuable because it can detect the presence of these components that traditional imaging methods can’t. There is a strong link between how strong the ITSS is and what the maximum rCBV is in the same tumor segments.[117] However, this correlation of ITSS and maximum rCBV also varies across different patients.[117] Since SWI gives off the strongest ITSS in glioblastoma, ITSS might be a useful tool for oncologists to make accurate glioma diagnosis. Researchers found out that SWI and DSC perfusion MRI have similar diagnostic and grading performance.[118] Again, compared to non-contrast SWI, contrast-enhanced SWI performs better in tumor evaluation.[119]

Conclusion

As it stands, the use of conventional MRI in neuro-oncology faces diagnostic difficulties that may be solved by emerging imaging techniques which, specifically, may better assess tumor subtypes and, especially, response to treatment.

Nonetheless, the emerging MRI techniques discussed here have unique limitations and challenges. For example, ADC aren’t stable for all types of tumors and treatments. For example, it works differently for antiangiogenic

therapy versus chemotherapy. Similarly, IVIM is sensitive to artifacts and different vessel sizes. DSC uses contrast agents, but contrast agents leakage often occurs, thus creating problems. DCE requires more prerequisites compared to DSC to be properly used, which makes its usage highly rigorous. Fortunately, ASL, the third perfusion MRI technique, CE SWI, and DKI all face insignificant obstacles.

Regarding these 7 cutting-edge techniques covered, their usefulness and limitations overlap with or accompany each other, suggesting that a variety of these techniques may provide the best picture of a patient's condition. For instance, ADC reflects diffusion, which is how well water flows in the patient's brain. This is different from perfusion, how well blood flows in the patient's brain. So to differentiate the two, IVIM could be used. It's important to differentiate the two because they provide different suggestions for oncologists. High diffusion means low cellularity, which means less malignant tumors. On the other hand, perfusion gives different measurements such as CBF, CBV, K-trans, and TTP, that reflects characteristics of blood vessels, which reflect how well a drug will perform. The three perfusion MRI techniques discussed here: DSC, DCE, and ASL, are all useful for predicting the efficacy of drug administration. DSC eliminates pseudoprogression which is important because less pseudoprogression means less false-positives evaluation on drug effects. DCE estimates immature vessels which is useful in predicting effectiveness of drug delivery. ASL provides CBF, which evaluates perfusion, which predicts effectiveness of drug delivery. Lastly, DKI and CE SWI can both be used to classify tumors, high-grade or low-grade. Thus, a consortium of advanced MRI techniques is likely to bring about the most effective treatment of brain cancer, from detection to remission.

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