

## Original article

### □ **Surgical calvarial demolition and reconstruction: procedure, implants and results**

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**SUMMARY:** In the surgical treatment of destructive pathologies of the cranium (intrinsic or contiguous), the demolition phase must be followed by a reconstructive procedure, preferably in the same surgical sitting. In this context, the task of the neurosurgeon has been greatly facilitated by the advent of custom-made cranial implants, which confer the following advantages: immediate restoration of the functional integrity of the cranium; excellent aesthetic outcome; rapid, safe and simple surgical procedure. Furthermore, when these implants are employed, the patient need only undergo one operation, rather than two. This is especially desirable, as the patient will not be exposed to the symptoms of "syndrome of the trephined" in the interim, neither will they face the psychological implications of having to endure an obviously deformed skull for several months (at least). Furthermore, customized cranioplasty implants are designed to fit, obviating the need for the surgeon to shape them during the procedure with curvature and thickness imperfections, and therefore considerably accelerating the process. Custom-made cranial prostheses can be made out of various materials, but acrylic resin (PMMA) and Porous HydroxyApatite (PHA) of varying degrees of porosity are most often used. While PMMA implants have the advantages of being less costly to produce and conferring a useful degree of primary mechanical resistance, PHA implants are biomimetic (biointeracting, biointegrating and biostimulating). Thanks to its osteoconductive properties, the use of hydroxyapatite has allowed us to achieve an optimal integration between the prosthesis and bone. The manufacture of custom-made cranial implants in porous PHA is an all-Italian technology that has been exported to the rest of the world. The use of this approach has consented excellent functional and aesthetic results to be achieved, even in the surgical demolition/reconstruction of large complex defects resulting from various destructive pathologies. In addition to the intrinsic difficulties in removing a tumour, surgery is further complicated by the need to create a hole in the skull that precisely conforms to the borders of the custom-made cranial implant, for this reason extensive use of the neuronavigator is advised. When faced with a demolition/reconstruction of the skull, the neuronavigator-assisted surgical procedure will entail the following series of steps: 1) the study of the three-dimensional resin model of the patient's skull, created from cranial CT data, to determine the precise area of bone to be demolished; 2) neuronavigational simulation of the surgical procedure, implementing both cranial CT and head MRI data; 3) validation of the cranial implant prototype that will be used to fill the cranial hole created during surgery. To aid the fitting of custom-made cranioplasty implants, the surgeon can take several measures to improve the chances of a long-term aesthetic and functional outcome. Among these is the use of "jigsaw" (intreflexions and extreflexions at the bone/implant interface) and "slanted S" (undulating profiles at the juxtaposition between two prostheses) techniques during

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*the implant design phase. It should also be borne in mind that could no longer find justification, and then also bring medical-legal implications, not providing the patient information of implant materials properties and procedural standards at the informed consent.*

**KEY WORDS:** *Calvarial demolition, Cranioplasty, Porous hydroxyapatite, Procedure.*

## □ Demolizione e ricostruzioni cranica: procedura, impianti e risultati

**RIASSUNTO:** *Nel trattamento chirurgico delle patologie destruenti interessanti il neurocranio (intrinseche o per contiguità), la fase demolitiva deve essere seguita da una procedura ricostruttiva, possibilmente nella stessa seduta operatoria. Nelle ricostruzioni la tecnologia “custom made” per la realizzazione di protesi craniche ha agevolato, non poco, il compito del neurochirurgo, facendogli raggiungere alcuni importanti obiettivi: immediata restituzione dell’integrità funzionale della scatola cranica; ottimale risultato estetico; procedura chirurgica rapida, semplice e sicura. Il realizzare in un unico tempo sia la demolizione sia la ricostruzione cranica con cranioplastica su misura porta ad alcuni indiscussi vantaggi anche per il Paziente stesso. Il Paziente si sottopone ad un unico intervento invece che due, evita il possibile verificarsi di una “sindrome del trapanato cranico” e non si espone ad un nocimento psicologico mostrandosi, per almeno alcuni mesi, con un cranio deturpato dalla craniolacunia. Il fatto poi di utilizzare solo cranioplastiche realizzate su misura evita di produrre dei manufatti con curvature e spessori non eseguiti a regola d’arte ed inoltre accelera, di non poco, la procedura. Le protesi craniche su misura possono essere realizzate in vari materiali, ma le più usate sono in resina acrilica (PolyMethyl Methacrylate: PMMA) o in idrossiapatite porosa (Porous HydroxyApatite: PHA) a vari gradi di porosità. Quelle in PMMA hanno il vantaggio di avere un processo di produzione meno costoso e di presentare una rilevante resistenza meccanica primaria, mentre quelle in PHA di essere biomimetiche (biointeragenti, biointegranti e biostimolanti). L’uso della PHA permette, inoltre, di raggiungere un obiettivo in più: l’ottimale integrazione osso-protesi, grazie al suo potere osteoconduttivo. La realizzazione di protesi craniche su misura in PHA è una tecnologia tutta italiana che è stata esportata nel resto del mondo. L’utilizzo di questa metodica ha permesso di ottenere ottimi risultati, funzionali ed estetici, in vaste ed impegnative demolizioni-ricostruzioni di superfici tecali interessate da varie patologie destruenti. Il tempo chirurgico presenta, oltre alle difficoltà intrinseche dell’asportazione tumorale, la necessità assoluta di realizzare una craniolacunia che permetta l’allogazione perfetta della protesi su misura e per questo viene consigliato l’uso estensivo del neuronavigatore. Nell’affrontare la patologia demolitiva-ricostruttiva del neurocranio, l’atto operatorio è condizionato e preceduto da una filiera di tappe preparatorie, quali: 1) lo studio del modello tridimensionale del cranio del paziente realizzato in resina partendo dai dati TC cranici al fine di disegnare il miglior perimetro dell’area tecale da demolire; 2) la simulazione al neuronavigatore della procedura chirurgica implementando sia i dati TC encefalici sia i dati RM; 3) validazione del prototipo della protesi cranica che andrà a colmare la craniolacunia che verrà realizzata durante l’atto chirurgico. Dalla nostra esperienza abbiamo tratto alcuni accorgimenti utili da implementare nel dispositivo su misura che consentono di ottenere facilitazioni, garanzie e migliori risultati durante la procedura chirurgica di inserimento della protesi. Fra questi l’applicazione delle tecniche “puzzle” (perimetro protesico con introflessioni ed estroflessioni) e ad “S italiana” (profili ondulati a livello della giustapposizione fra due protesi) durante la fase di progettazione della protesi. Va infine tenuto presente che potrebbe non trovare più giustificazione, e quindi portare anche una implicazione medico-legale, il non fornire al Paziente, al consenso informato, notizie su tali potenzialità e standard procedurali.*

**PAROLE CHIAVE:** *Demolizione cranica, Cranioplastica, Idrossiapatite porosa, Procedura.*

## □ INTRODUCTION

Custom-made implants, for both direct cranioplasty and single-sitting demolition/reconstruction of the skull affected by a destructive pathology (in particular meningiomas and metastases) has now become standard operating practice, conferring significant advantages for the patient, surgeon and healthcare provider alike<sup>(39)</sup>. The entire process, from acquisition of the images to creation of the prototype to implantation of the final prosthesis in the patient, is aided by

the extensive use of Digital Imaging and COmmunications in Medicine (DICOM) images, Computer-Aided Design (CAD) and Computer-Aided Manufacture (CAM), implemented by means of the neuronavigator<sup>(10,14,15,36,46)</sup>.

The use of imaging is of primary importance in single-procedure cranial demolition/reconstruction, and it is heavily exploited in the following stages of the protocol:

1. creation of a made-to-measure prosthesis using patient specific CT data;

2. programming the neuronavigator, inputting CT images of both direct head MRI data and a 3D resin model of the patients skull (*see "Surgical Procedure"*);
3. neuronavigator-assisted surgical demolition of the skull section<sup>(28,43)</sup>.

In this article we aim to provide a summary of that which should be considered a must in destructive processes of the skull: single step demolition/reconstruction using made-to-measure cranioplasty implants. In this context we go on to highlight that the extensive use of the neuronavigator is practically indispensable, in both the design of the implant and the creation of its cranial housing.

## □ PATIENTS

From February 2004 to February 2010, 57 cranioplastic procedures were performed at Udine University Hospital using custom-made implants, almost all of which were made of Porous Hydroxy-Apatite (PHA). 17 of these cases featured demolition/reconstruction due to destructive lesions of the skull, and three of these required two implants due to the extensive nature of the lesions.

DICOM images, manipulated by CAD and CAM, were heavily exploited in the manufacture of these prostheses, from the initial acquisition of the images to the manufacture of the prototype and the implant itself. All surgical procedures were performed with the aid of a neuronavigator.

Noteworthy complications arose in two cases: ischaemic necrosis of the skin flap (in a patient previously operated on several times for meningioma and infection of the operculum a decade before; the issue was resolved by flap rotation after prostheses removal) in one instance, and one case of infection of the soft tissues overlying the cranioplasty implant (in this case the prosthesis was conserved after suitable prolonged antibiotic therapy).

## □ PURPOSE AND TIMING

Although less than 2% of all bone tumours involve destructive lesion of the skull, these cases are considered particularly challenging in neurosurgery, as the surgeon must not only remove the affected bone (demolition phase), but also to repair the skull hole using cranioplasty (reconstruction phase)<sup>(32,60)</sup>.

Broadly speaking, these lesions involving the cranial bones can be subdivided into:

- primary or secondary malignant or benign tumours,
- non-neoplastic lesions<sup>(60)</sup>.

Benign primary lesions include osteoma, chondroma, giant cell tumours, haemangioma and lymphangioma, and their malign counterparts include osteogenic sarcoma, fibrosarcoma, chondrosarcoma and chordoma<sup>(3,9,16,40,45)</sup>. Among the secondary lesions affecting the skull are, obviously, metastases (from the lung, breast, kidney, thyroid or prostate), as well as lymphoma, multiple myeloma, neuroblastoma and Ewing's sarcoma<sup>(3,9,16,40,45)</sup>. Secondary involvement of the skull can also arise in processes affecting the contiguous structures, such as meningioma and paraganglioma. In addition, the cranial bones can be affected by proliferative or paraneoplastic lesions, i.e. Paget's disease, histiocytosis, fibrous dysplasia, hyperostosis and mucocoeles, etc.<sup>(3,41,49)</sup>.

In order to remove areas of affected cranial bone, the demolition and reconstruction (cranioplasty and repair of the dura, where necessary) phases can be performed in sequence during the same surgical sitting or, in increasingly rare cases, in two operations performed at different times<sup>(39,43,60)</sup>.

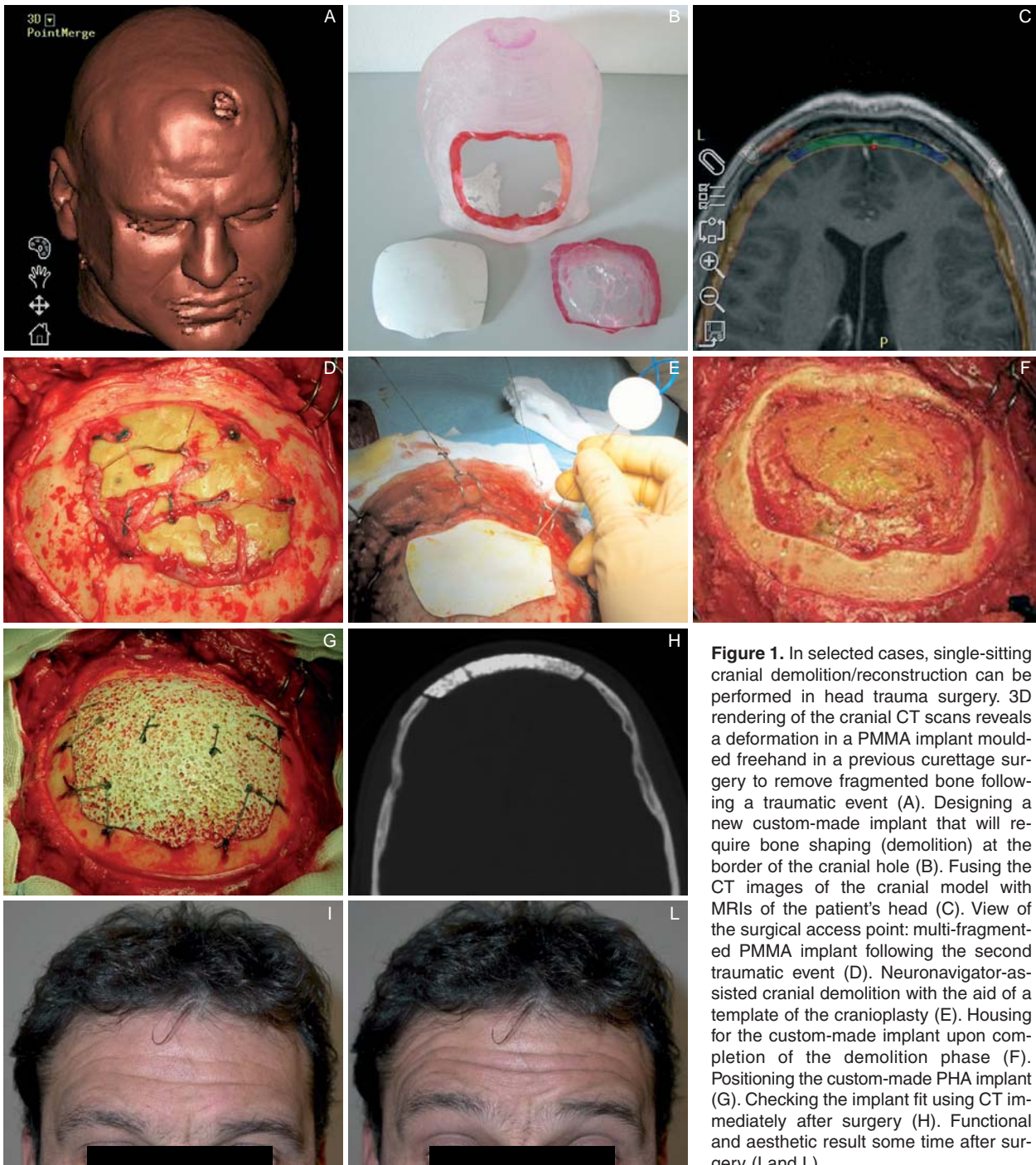
The single sitting demolition/reconstruction approach can be applied not only to cranial expansion processes, but also to the repair of congenital cranial defects<sup>(12)</sup> or those resulting from decompressive craniectomy (performed to relieve intracranial hypertension)<sup>(60)</sup>, in cases where the marginal bone needs to be reshaped to provide satisfactory aesthetic and functional outcome. In fact, in decompressive craniectomy and post-traumatic toilet to remove fragments of bone are generally performed with extreme urgency, and providing adequate housing for the subsequent implantation of a prosthesis is not high on the list of the operating surgeon's priorities. Hence, the craniectomy margins may need to be remodelled in these cases, which are ideal opportunities for the application of the custom design, manufacture and fitting of prostheses at a single sitting (Figure 1).

Although cranioplasty implants can be sculpted free-hand while the operation is underway, this time-consuming and risk-enhancing process is considerably curtailed to minor adjustment of a custom-made implant, purpose designed weeks or months before the surgical sitting.

The advantages of surgery performed at a single sitting are evident, namely:

- one operation rather than two,
- less risk and discomfort for the patient,





**Figure 1.** In selected cases, single-sitting cranial demolition/reconstruction can be performed in head trauma surgery. 3D rendering of the cranial CT scans reveals a deformation in a PMMA implant moulded freehand in a previous curettage surgery to remove fragmented bone following a traumatic event (A). Designing a new custom-made implant that will require bone shaping (demolition) at the border of the cranial hole (B). Fusing the CT images of the cranial model with MRIs of the patient's head (C). View of the surgical access point: multi-fragmented PMMA implant following the second traumatic event (D). Neuronavigator-assisted cranial demolition with the aid of a template of the cranioplasty (E). Housing for the custom-made implant upon completion of the demolition phase (F). Positioning the custom-made PHA implant (G). Checking the implant fit using CT immediately after surgery (H). Functional and aesthetic result some time after surgery (I and L).

- more immediate functional and aesthetic recovery. Furthermore, there are several secondary advantages that should not be ignored; indeed, shorter operating times do not only translate into less risk for the patient (anaesthesia, exposure to infection, exothermic reactions, etc.), but also considerably reduce the workflow of the surgeon, anaesthetists, and theatre per-

sonnel. This obviously confers a significant financial saving, which needs to be weighed against the increased cost of a custom-made prosthesis. In this context, however, it is important to bear in mind that a monetary value cannot be placed on the satisfaction (or health) of the recipient of a well-performed procedure.

## □ MATERIALS

The ideal cranioplasty implant will have marked biomimetic properties (biointeraction, biointegration and biostimulation)<sup>(29)</sup>. At present, only PHA (Figure 2) possesses these features<sup>(26,27,35,54)</sup>, although in some cases the greater impact strength and wear resistance provided by PolyMethyl Methacrylate (PMMA) (Figure 3) may be indicated<sup>(22)</sup>. In fact, PMMA possesses ten-fold resistance to flexure and compression with respect to PHA (100 MPa vs. 7-13 MPa, and 35 MPa vs. 2.5-3.5 MPa, respectively) and almost double its elasticity (16 GPa vs. 9-10 GPa). PMMA has similar properties to cortical bone (porosity 5-10%, resistance to compression 131-205 MPa, resistance to flexure 49-148 MPa and elasticity 11-17 GPa); PHA, on the other hand, is more similar to spongy bone (porosity 50-80%, resistance to compression 1.6 MPa, negligible resistance to flexure, and elasticity 9-32 GPa)<sup>(27,34)</sup>.

Indeed, although PHA is a synthetic bioceramic, it possesses the same chemical formulation as bone micro crystals, and consequently the same Ca/P ratio as bone tissue. Its osteoconductivity is directly proportional to its porosity, and its pores can vary in terms of size, number and type of interconnections (60-70% porosity with macropores diameter of the order of 200-500  $\mu\text{m}$ , 1-10- $\mu\text{m}$  micropores and 50-200- $\mu\text{m}$  interconnection spaces); the greater the degree of porosity and interconnection, the better the osteoconductivity.

PMMA on the other hand is a plastic material formed from methyl methacrylate polymers, methacrylic acid esters. It has been known for many years, since its development in several laboratories in 1928 and its debut on the market in 1933, courtesy of the industrial chemistry firm Röhm. As early as 1940, after various experiments on animals revealed no particular adverse reactions, the use of PMMA to make cranioplasty implants began<sup>(44,58)</sup>.

## □ PROSTHETIC OPTIONS

Except in exceptional cases, cranial implants should all ways be custom-made. This is because the task of the modern surgeon is not only to treat, and possibly to heal, the patient, but also to restore them to their former or ideal condition (*restitutio ad integrum*) in terms of both function and aesthetics. Nevertheless, it should not be forgotten that the manufacture of a cranioplasty implant is not governed by clinical considerations alone; instead, various medicolegal rami-



**Figure 2.** Custom-made PHA prosthesis. Note the rough surface due to the micro- and macropores and fixing holes. This architecture provides relatively poor impact resistance in the short term but promotes osteomimesis. The perimetral anchorage and dural suspension fixation holes are visible at the edges and centre of the implant, respectively.

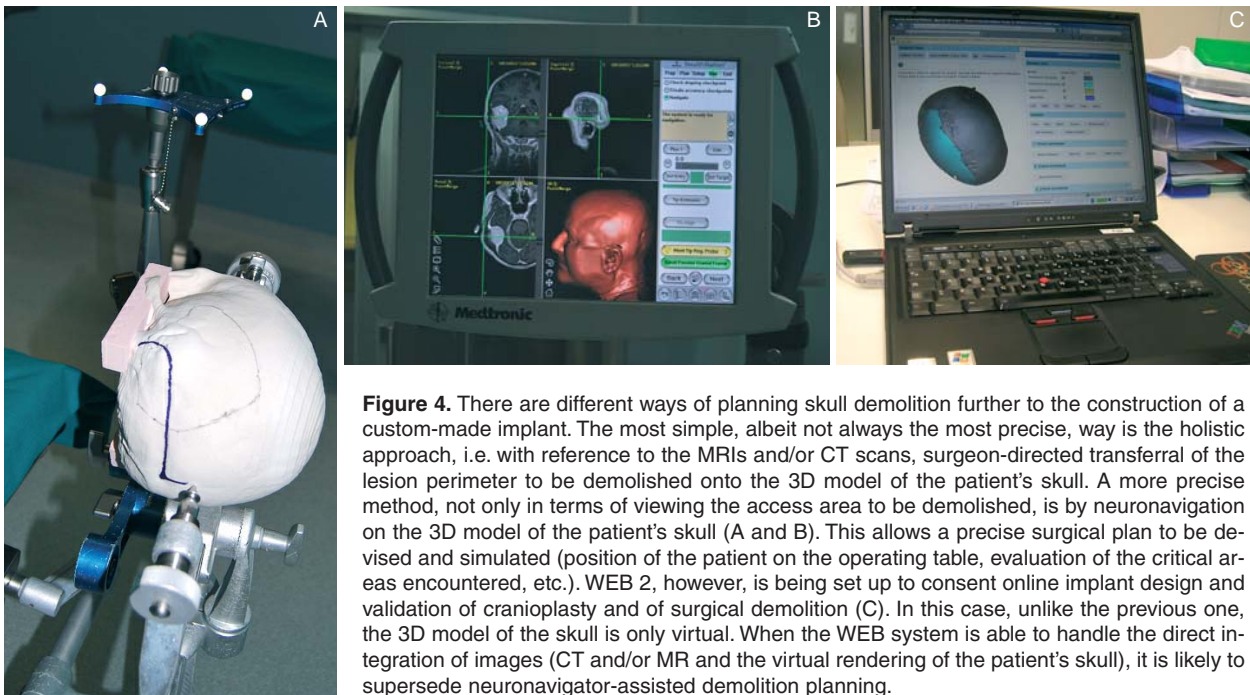


**Figure 3.** PMMA implant. Confers high impact resistance, but the surgeon must drill numerous holes penetrating the entire thickness of the implant to promote adhesion to the biological substrate.

fications need to be taken into account, in particular the right of the patients to be fitted with the most suitable prosthesis for their case. Hence, if a particular implant is judged to be of better quality and to reduce the risk to the patient, it must be included among the treatment choices offered them, as healthcare is an unalienable right that should not be compromised by financial considerations<sup>(17)</sup>.

In the specific case, during informed consent, the patient must be made aware not only of matters concerning the demolition surgery (type of lesion, surgical technique, any nonsurgical treatment alternatives,





**Figure 4.** There are different ways of planning skull demolition further to the construction of a custom-made implant. The most simple, albeit not always the most precise, way is the holistic approach, i.e. with reference to the MRIs and/or CT scans, surgeon-directed transferral of the lesion perimeter to be demolished onto the 3D model of the patient's skull. A more precise method, not only in terms of viewing the access area to be demolished, is by neuronavigation on the 3D model of the patient's skull (A and B). This allows a precise surgical plan to be devised and simulated (position of the patient on the operating table, evaluation of the critical areas encountered, etc.). WEB 2, however, is being set up to consent online implant design and validation of cranioplasty and of surgical demolition (C). In this case, unlike the previous one, the 3D model of the skull is only virtual. When the WEB system is able to handle the direct integration of images (CT and/or MR and the virtual rendering of the patient's skull), it is likely to supersede neuronavigator-assisted demolition planning.

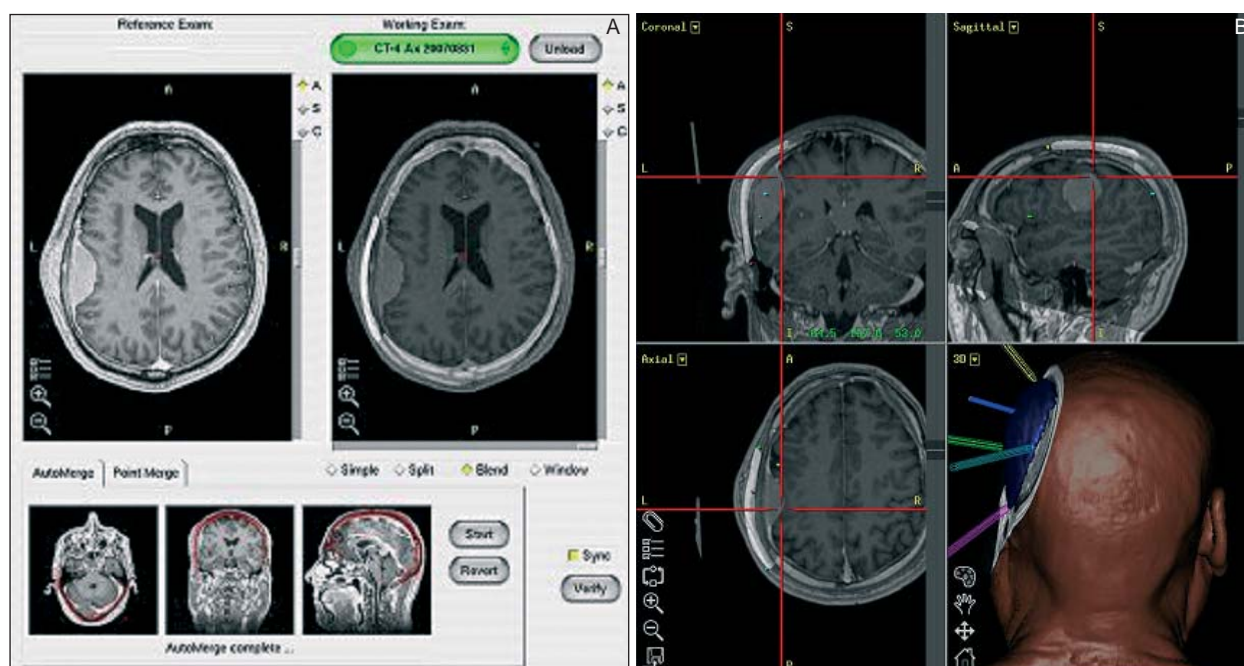
complications, etc.), but also the options available for reconstruction (freehand or custom-made implants, etc.). This process of informing the patient must also include a detailed description of the types of material that can be used, with an explanation of their relative benefits and drawbacks (fragility, unsightliness, etc.), as well as the relative risks (infections, reabsorption, decubitus, rejection, etc.). Based on these considerations, PHA should be the material of choice unless patients are not expected to live long, experience frequent epileptic falls, or have been diagnosed with a serious psychiatric illness. Likewise, in institutionalised patients who are prone to violent behaviour, PMMA may be more suitable<sup>(58,60)</sup>. Nevertheless, in this rapidly advancing field, materials such as PolyEther Ether Ketone (PEEK) and caprolactone are also proving in cases where immediate mechanical resistance is required.

## □ SURGICAL PROCEDURE

Nowadays, the procedures involved (CT scanning and production of the 3D resin prototype; three-dimensional evaluation of the defect and creation of an implant prototype) in creating a custom-made cranioplasty prosthesis are well established<sup>(28)</sup>. The procedure features three main steps:

1. *fabrication of a custom-made prosthesis*, involving:
  - *data acquisition*: thin-slice CT scans of the skull saved in DICOM format;
  - *data processing*: computerised three-dimensional rendering of the digital CT images;
  - *model manufacture*: stereolithographic production of a 1:1 scale three-dimensional resin reproduction of the skull;
  - *implant design*: the neurosurgeon delineates the part of the skull to be demolished on the resin model;
  - *prototype manufacture*: according to the neurosurgeons specifications;
  - *prototype validation*: the neurosurgeon approves the 3D resin model, indicates where perforation should be made for fixing and dural suspension, and makes any volumetric corrections necessary to compensate, for example, for muscle atrophy;
  - *fabrication and sterilization of the implant*: a block of porous hydroxyapatite is shaped to conform to the approved prototype and the finished implant is sterilized.

The implant design procedure in demolition/reconstruction cases is identical to that in simple cranioplasty, featuring only one additional step: *delineation of the area to be removed*, comprising the entire lesion site and a safe perilesional mar-



**Figure 5.** CT images of the 3D cranial model with the approved prosthesis are fused with head MRIs by the neuronavigator software (A). The neuronavigator provides a 3D view that enables neuronavigator-assisted surgery and a more precise demolition, in spatial and implant housing terms, with respect to the usual anatomical reference points only (B).

gin. In delineating this area, especially in cases in which the pathological skull surface is indistinguishable from the surrounding outer table of cortical bone, the surgeon will need to consult the information provided by the neuroradiological images (CT and MRI), both from standard scans and the neuronavigator, and the 3D digital rendering of the skull (Figure 4). This procedure will soon be greatly facilitated by the WEB 2 website, currently in an advanced stage of development, which will enable the surgeon to interface directly with the prototype manufacture online. This website will considerably accelerate production times and will consent meaningful dialogue between the surgeon and technician in real time, without having to resort to intermediaries.

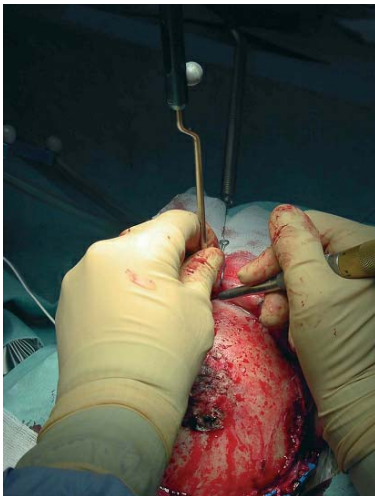
2. *preparation of the neuronavigator.* Once a definitive 3D resin model of the skull and defect has been produced, it will be scanned by CT, and the resulting images, together with head MR (or in some cases CT) images of the patient, are loaded into the neuronavigator (Figure 5). The process by which this is achieved will depend on the neuronavigator model employed and the resolution of the images themselves - in some cases it is entirely automatic, while in others the operator will be

called upon to input the reference points to impose on both sets of scans.

The routine use of the neuronavigator in cranial demolition/reconstruction consents optimal fitting of the cranioplasty implant in the skull hemisphere with a precision that is difficult to achieve relying on anatomical reference points alone. In fact, in every instant the neuronavigator provides coordinates in the three dimensions of space.

Furthermore, when removing tumours in the motor and speech areas, the DICOM data furnished by the CT of the 3D resin model can be fused to the patient's functional MRI data (fMRI)<sup>(4,13,47,60)</sup>; this enables the neuronavigator to accurately perform the incision, cranial demolition (navigator probe on the craniotomy drill), tumour excision (brain mapping) and correct fitting of the cranioplasty implant.

3. *neuronavigator-assisted surgical demolition.* The complexity of this operation can vary, but even in the incision phase, the neuronavigator can help plan the access phase<sup>(60)</sup>. However, it is in the subsequent phase of bone demolition that the tool makes itself particularly useful: its pointer probe tip can be used simply to delineate the area of bone to be removed, relying on certain spatial coordinates



**Figure 6.** It is easy to delineate the perimeter of the demolition site using the neuronavigator probe.



**Figure 7.** The neuronavigator probe may also be used as a drill. In this case the demolition can be accelerated, allowing the operator to view the precise perimeter of the site to be demolished on screen and in real time.

(Figure 6), or the drill itself can be used as a probe (Figure 7). In this case, optical position sensors (little reflecting spheres) are mounted on the drill, and the information transmitted to the neuronavigator is displayed onscreen, thereby enabling precise circumscription and demolition of the diseased bone.

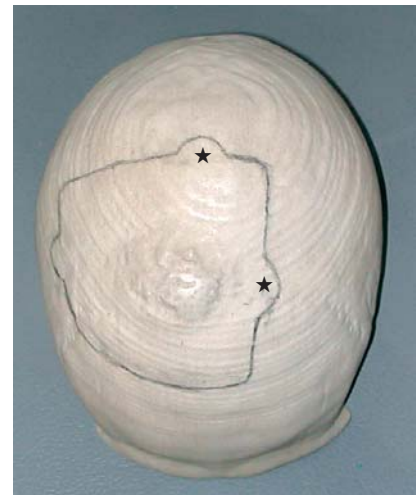
**□ PLANNING CONSIDERATIONS**

Various complications may arise after the positioning of a cranial implant, and the surgeon must keep these

in mind in the planning phase. Perhaps the most feared of these adverse events is the dislocation of the prosthesis itself, which will necessarily require further surgical intervention<sup>(55)</sup>. It is therefore good practice to seek to avoid this eventuality when the implant is being designed. In order to reduce the possibility of the implant coming adrift, the junction it forms with the cranial bone should mirror the natural cranial sutures, i.e. incorporate a dovetail or sawtooth effect (Figure 8). Although the physiological irregularity of this type of joint is difficult to replicate in a surgical setting, a surgeon can employ the “jigsaw” technique, serrating the edge of the prosthesis in such a way as



**Figure 8.** Cranial sutures showing dovetail and sawtooth processes. This architecture is also a point of reference in the design of custom-made cranial implants, to prevent their dislocation, a possible complication.



**Figure 9.** Delineation of the area to be demolished on the 3D model of the patient's skull. The “jigsaw” technique reduces the likelihood of implant dislocation. Where possible, extroflexions on the borders of the custom-made implant should be made at the sutures (★) to exploit these fixed anatomical reference points.



to fit the borders of the craniectomy hole and create other topological features that will also aid implant positioning (e.g. extroflexions on the borders of the implant at the sutures in order to have rapid and sure anatomical landmarks)<sup>(1,48,57,59)</sup> (Figure 9). Although the neuronavigator greatly assists spatial positioning of the prosthesis, using the cranial sutures as a point of reference for this jigsaw design will undoubtedly further aid optimal orientation in the demolition phase.

Likewise, when two adjoining cranial implants are required, it is vital that their margins of contact are specularly designed to follow the shape of a “slanted S”, i.e. not straight, which will greatly aid their precise juxtaposition<sup>(48)</sup> (Figure 10).

These precautionary measures, together with the bevelling with a 45° angle applied to the edges of both the implant and the skull hole, should be sufficient to prevent the prosthesis sinking or becoming dislocated altogether<sup>(48,57,59)</sup> (Figure 11).

Practically, the custom-made cranioplasty fits into the prepared hole in the skull like a piece of a jigsaw, becoming a whole - at first mechanical and later biological - with the rest of the cranium.

#### □ PRECAUTIONARY MEASURES

When planning surgical demolition/reconstruction, it is necessary to consider a flap that will not compromise the final aesthetics or damage the local anatomical structures. Hence, zigzag margins (resembling the hairstyle of the members of the television’s famous cartoon family, The Simpsons) (Figure 12) are essential and encroaching beyond the hairline is to be avoided, as is involving the main arterial trunks, and the temporal muscle, positioned over the implant and anchored in the vicinity of the sagittale line of the head (Figure 13), should be damaged as little as possible in order to reduce the risk of atrophy. This becomes important in the subsequent reconstructive phase, conferring better aesthetic and functional (mastication) outcomes, as well as consenting better osteointegration of the custom-made implant, whose fixing will complete the single-sitting procedure<sup>(59)</sup>.

#### □ EVALUATION OF OSTEOINTEGRATION

All types of hydroxyapatite possess excellent biocompatibility and, when fitted in direct contact with

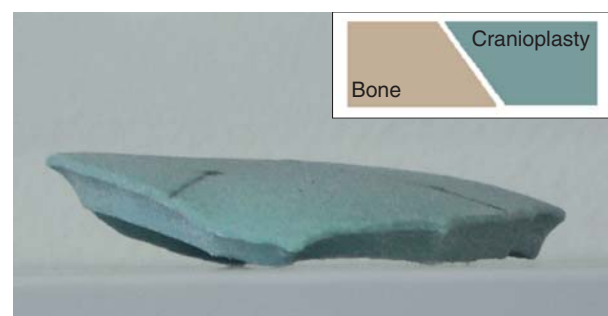
**Figure 10.** In large cranial holes of pronounced curvature, it may be necessary to fabricate custom-made PHA cranioplasties in two pieces. To prevent sliding, the implants are designed so that they fit together in the shape of a “slanted S”.



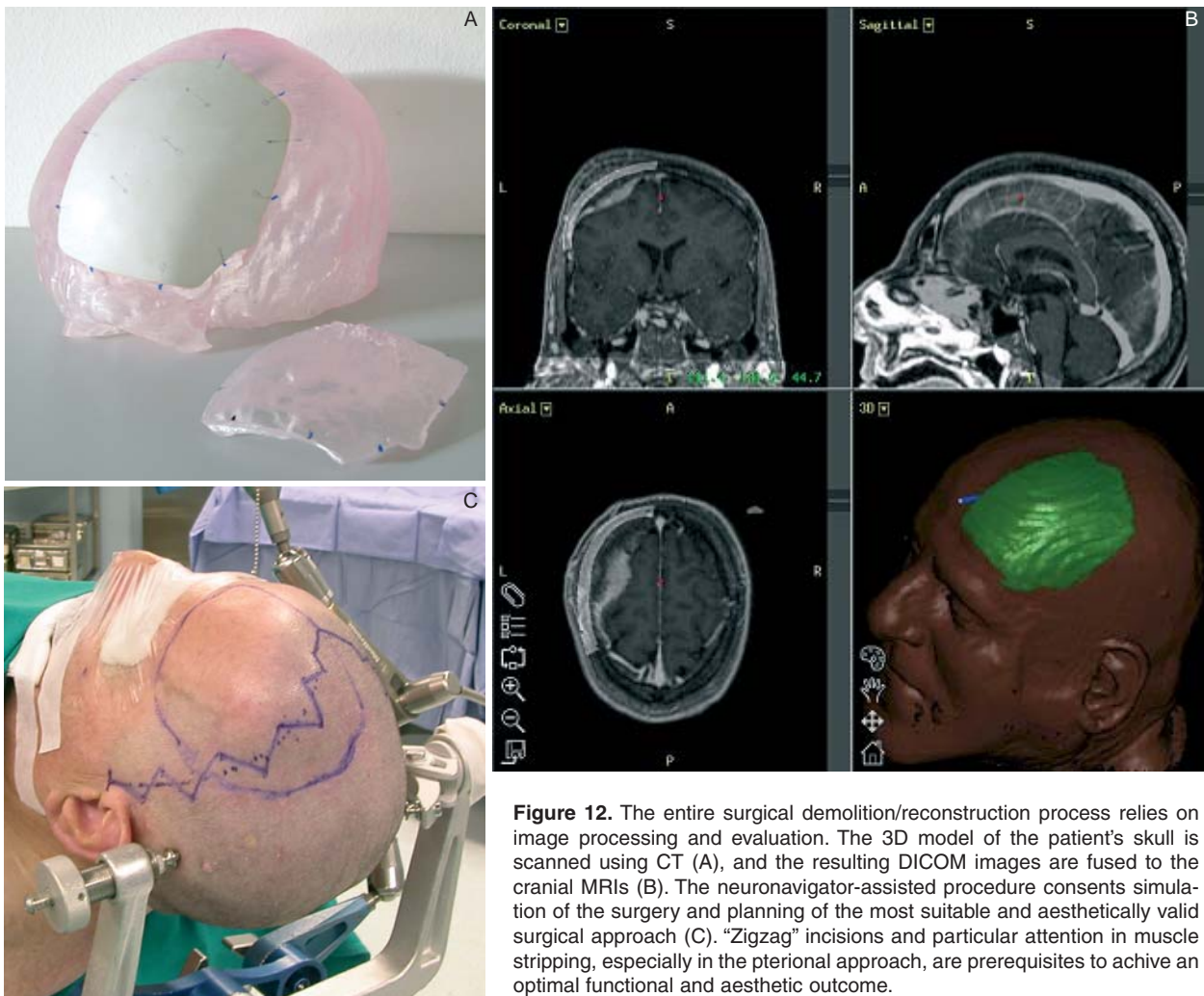
the bone, show osteoconductance, osteointegration and, in the presence of bone growth-inducing factors, even osteoinduction. PHA has a three-dimensional spongy structure of interconnected pores, perfectly mimicking the mineral component of bone, in particular the spongy tissue where bone cell regeneration occurs upon fracture.

The principal advantage of PHA is the growth of fibrous bone tissue inside its cavities, which enables its physical integration with the surrounding bone within a matter of weeks or months. When the growth of this fibrous bone tissue is complete, the implant is made up of roughly 17% bone, 43% soft tissue and 40% PHA<sup>(19)</sup>.

In order to evaluate the degree of osteointegration between the PHA prosthesis and the surrounding bone, CT scans are usually employed with bone viewing windows<sup>(56)</sup>. Nevertheless, this technique is not without its critics in that, even with small variations in



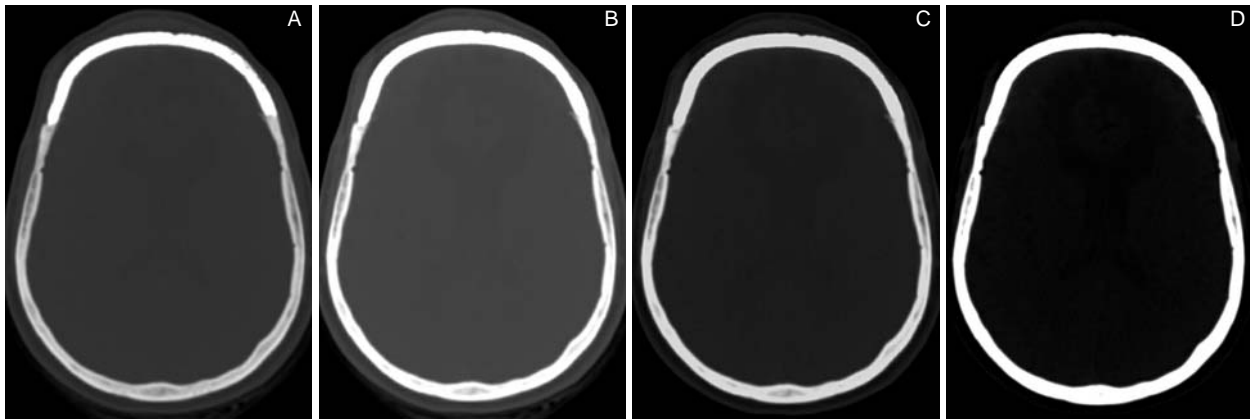
**Figure 11.** The implant perimeter must have a 45-degree bevelled edge, and the edge of the bone demolition site shaped to fit. This will prevent the custom-made prosthesis sinking.



**Figure 13.** A precaution is to avoid anchoring the prosthesis to the temporal muscle, as this should, instead, be positioned over the implant and anchored in the vicinity of the sagittal line of the head.

bone window range, the degree to which the continuity between prosthesis and bone is evident changes (Figure 14). Furthermore, little or no information regarding the actual degree of ossification in areas not immediately adjacent to the implant edges. Nevertheless, an indirect evaluation that this can occur has been furnished by cases of implant fracture some time after fitting, in which CT has been used to document that a fracture with well juxtaposed edges, despite crossing the entire prosthesis, healed completely within the space of a few months<sup>(37,38)</sup>.

More valid methods of quantifying integration of the implant rely on nuclear medicine. In fact, scintigraphy series over the time are able to establish the degree of radiotracer accumulation and therefore map the penetration of the bony tissue in the prosthesis. To this end, <sup>99m</sup>Tc methylene diphosphonate (medronic acid, MDP), routinely used in bone scintigraphy and



**Figure 14.** The most simple and widespread means of evaluating implant osteointegration is cranial CT with bone windows. One of the limitations of this technique is that varying the viewing windows may change the perception of the degree of osteointegration.

SPECT, can be exploited to evaluate the activity of the osteoblasts. Even more promising is the use of positron-emission tomography (PET) in conjunction with fluorine-18, which confers the additional advantages of better resolution, higher sensitivity and the possibility of using CT imaging.

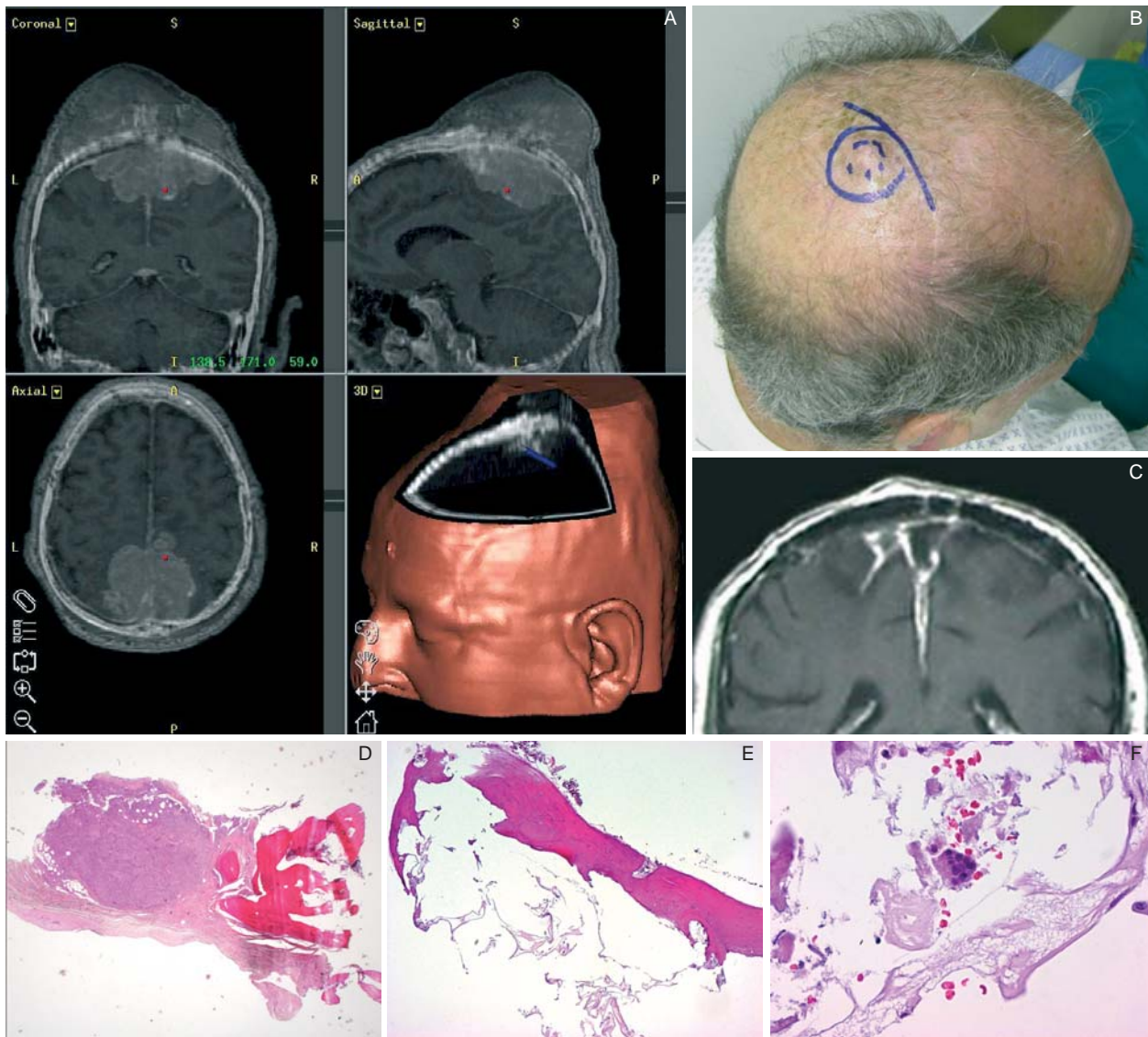
Nevertheless, it is histological examination that confers direct confirmation of the state of osteointegration of the PHA prosthesis. However, at present, it is only by means of animal sacrifice studies that we are able to use this method to evaluate the histology of appositely implanted prostheses. Clearly analogous assessments are ethically unfeasible in man, and the only information we have, supplied by the study of implants removed following dislocation, fracture or infection, are inconclusive in that, by their very nature, their osteomimetic capacity was compromised by poor positioning or suppurative complications.

Nonetheless, we have been able to reveal that this osteointegration does occur away from the edges of PHA prostheses. In one patient, re-operated on due to the regrowth of an atypical meningioma at the cranial vertex, we discovered not only that the tumour had penetrated the PHA scaffold of the previously fitted implant, but also that osteoblasts had permeated throughout the entire structure (over 15 cm in diameter), even reaching its centre (Figure 15). Hence, the particular composition and architecture of PHA appear to confer excellent osteomimetic qualities to cranioplasty implants, enabling bone regeneration not only at the bone/PHA interface, but also some distance from it. This process can be greatly aided by several process used in engineering of the prosthesis itself.

#### □ PROSTHESIS ENGINEERING

As well as conferring excellent osteointegration, PHA rarely provokes an immune response. Nevertheless, these implants are extremely fragile, i.e. they tend to break rather than bending. In fact the yield strength of this material (the stress at which it begins to deform plastically) is very high and coincides with its breaking strain. These physical and mechanical properties means that until new bone is laid down within the PHA scaffold, the implant is more vulnerable than the bone that it was designed to mimic and replace. However, rather than replacing the material used to create the scaffold, which has proved extremely fit for purpose from a biological perspective, researchers are attempting to find ways of potentiating the process of both osteoblast and osteoclast invasion throughout the scaffold, thereby accelerating osteoconduction and increasing the mechanical resistance of the implant to at least that of the surrounding bone. Thus, the first obstacle to overcome is how to accelerate bone tissue regeneration. One way of doing this could be to engineer PHA implants to contain platelet-rich plasma gel and/or bone marrow-derived stem cells<sup>(7,23,24,31,50)</sup>. Platelet-Rich Plasma (PRP) is produced by removing red blood cells from peripheral blood, yielding a final composition of platelets and growth factors (4-6-fold physiological concentrations); fibrin (physiological concentration) and red blood cells (15% less than physiological concentrations). Stem cells on the other hand are prepared by removing red blood cells from bone marrow (usually aspirated from the iliac crest), leaving a final product



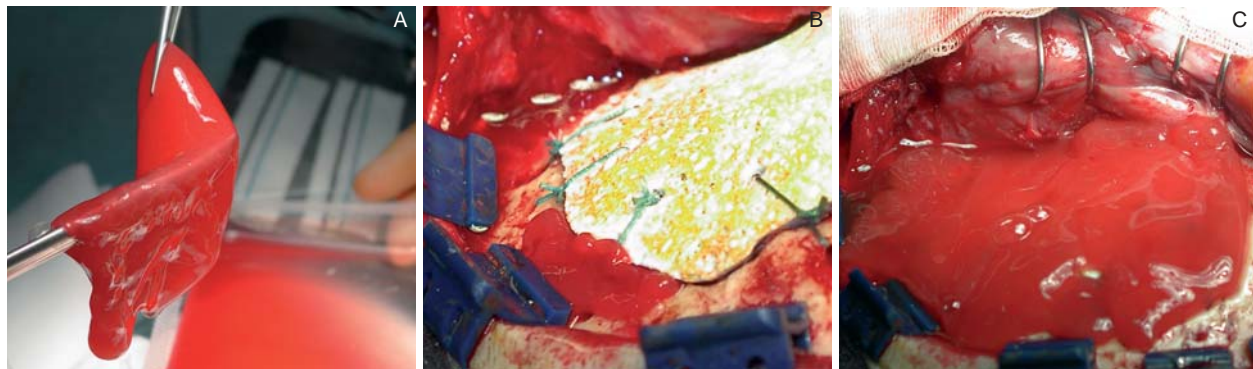


**Figure 15.** 60-year-old patient operated on in 2004 for a large atypical meningioma at the vertex and osteoid reaction of the cranial vault (A). Single-sitting surgical demolition/reconstruction of the skull and fitting of a custom-made PHA cranioplasty implant. 4 years later the patient underwent another operation due to a small meningioma relapse at the centre of the implant (B and C). Histology (D) showed newly formed lamellar bone tissue at the same site as the cancerous meningioma tissue. The material under examination (E and F) was made up of a minute flap of fibrosclerotic tissue, together with several micro-shards of lamellar bone tissue accompanied by amorphous reticular tissue (PHA, implant), in which a few giant polynucleated osteoclastoid cells are also visible. In the long term, osteomimesis also occurs in the areas distant from the bone/implant interface. Bone deposition in the PHA implant usually occurs in a “leopard print” pattern. (We thank Dr. Stefano Pizzolitto, Department of Pathology, General University Hospital, Udine, Italy, for the histopathology preparations.)

composed of: haematopoietic and mesenchymal stem cells; vascular progenitors; immune cells and platelets.

The biological properties of PRP, i.e. its capacity for promoting tissue regeneration, stem from the growth factors it contains, which in concert with the other numerous different molecules released from activated

platelets. Among the growth factors contained in platelets, the activities of PDGF (Platelet-Derived Growth Factor), TGF- $\beta$  (Transforming Growth Factor beta), EGF (Epidermal Growth Factor) and IGF I and II (Insulin-like Growth Factor) have been well documented<sup>(8,20,23)</sup>; these factors actively contribute to the stimulation and replication of cells,



**Figure 16.** In order to accelerate osteoinduction it is possible to engineer the prosthesis using a platelet-rich plasma gel rich in growth factors (A). This PRP gel can be inserted either at the junction between the bone and prosthesis (B) or covering the entire surface of the implant (C).

thereby promoting the formation of new bone tissue. Stem or stromal cells from the bone marrow, in relation to the surrounding tissue environment, can generate chondrocytes, osteoblasts, adipocytes, myoblasts and endothelial cell precursors, and serve for the repopulation of bone grafts. It is therefore possible to accelerate osteoinductive processes by spreading a layer of PRP gel or stem cells over the surface of the implant.

A film of PRP (which can be enriched with granules of PHA) can also be inserted between the perimeter of the PHA implant and the bone border (Figure 16 and 17) to accelerate and augment the osteomimetic process of the prosthesis in both quantitative and qualitative terms<sup>(2,21)</sup>. This can be measured by neuro-radiological follow-up and nuclear medicine. The normal phases of osteointegration of PHA prostheses requires approximately 1-2 years, depending on the

size of the implant itself and the individual characteristics of the patient. This period can be reduced by 30%, and even as much as 50% and over, with the appropriate use of growth factors.

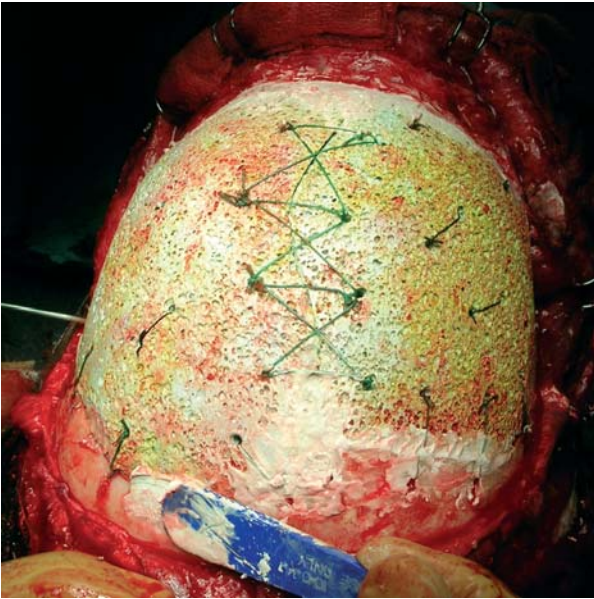
#### □ FILLING

On occasion, when drilling bone, technical error of removing too much tissue may occur, preventing the custom-made cranioplasty implant from perfectly adhering to the bone perimeter. Likewise, the surgeon may also discover mid-operation that more bone than was planned during the implant design phase must be removed, as an area of pathological bone cannot be left in situ. In these cases, filler may be required to plug the gap between implant and bone. A particularly versatile soft bone filler appears to be calcium



**Figure 17.** The PRP gel can be enriched with granules of PHA (A). These spherical granules are characterized by an interconnected porosity in the range 5-50 mm. The amalgam of gel and granules can be inserted at the join between the bone and the custom-made cranioplasty implant (B, C).





**Figure 18.** Malleable bone filler substitute can be used to plug any gaps. Mixing calcium phosphate powder yields a soft paste that hardens within a few minutes and is ideal for manual moulding and shaping with a burr.

phosphate powder<sup>(11,25,57)</sup>. Mixing this with an aqueous solution of sodium phosphate yields a paste that can be manipulated for use in finishing and structural reinforcement of cranioplastic reconstructions, as well as filling small holes in the craniofacial skeleton and plugging the skull base or frontal sinus. This paste hardens in a few minutes and, once crystallized, can be abraded and shaped with a burr (Figure 18). As its composition is very similar to that of bone, this os-

teoconductive material is an excellent scaffold, allowing the penetration of osteoblasts and osteoclasts and therefore favouring deposition of new bone<sup>(30)</sup>.

#### □ SKIN

Cranial reconstruction does not end with the fitting of the cranioplasty, and can only be considered a complete success if it is covered by complete and functional soft tissues. To favour recovery of cutaneous trophism, and in order to prevent possible complications following implantation, the insertion of a biological membrane, a dermal matrix, between the prosthesis and the skin flap has been used<sup>(57)</sup> (Figure 19). The dermal matrix is a semi-biological, non-living implant comprising a single-layer membrane, a porous leaf of reticulated collagen from bovine Achilles' heel tendon, and glucosaminoglycan (chondroitin 6-sulphate). This matrix triggers a histoinductive and histoconductive action on the mesenchyme, guiding the formation of healthy dermis<sup>(5,42,51-53)</sup>.

The use of a dermal matrix as a device for thicken the scalp above a PHA implant is indicated in cases of cutaneous hypotrophy and thinness due to repeated surgical interventions, radiation treatment, flap for complex scalp defect and post-traumatic scarring. In a very thin scalp, the simple positioning of a dermal matrix over a custom-made PHA cranioplasty implant seems to improve and guarantee long-term aesthetic and functional results of cranial reconstruction surgery, as it not only increases the protective role of the soft tissues, but also promotes local new vascularization, which can improve the trophism of the



**Figure 19.** To ensure the success of a cranioplasty implant, the trophism of the overlying soft tissues is vital. In cases of cutaneous hypotrophy, a dermal matrix can be inserted between the surface of the implant and the bottom layer of the skin. The dermal matrix is a single-layer membrane composed of reticulated collagen and glucosamine glycan. This mesh promotes histoinduction and histoconduction of the mesenchyme, and favours the local formation of new blood vessels, which can exert a beneficial influence on the osteointegration of the implant itself.



cranioplasty implant itself<sup>(18,41)</sup>. In cases where a dermal matrix has been used in this fashion, head MRI has revealed that dermal trophism is much improved with respect to the pre-surgical situation even after a few weeks.

#### □ RADIOBIOLOGY

Patients treated by removal of a destructive lesion of the skull and fitted with a cranioplasty implant will often require not only neuroradiological follow-up but also subsequent radiotherapy. In this context, experimental acquisitions have revealed that PHA is an extremely effective shield against ionizing radiation; dosimeters placed just under the prosthesis show exposure to higher radiation doses when PMMA rather than PHA implants are used<sup>(8)</sup>. This must be taken into account by those scheduling radiotherapy after surgery as part of the treatment plan.

#### □ SUBSEQUENT SURGERY

Refinements in techniques and increased life expectancy make it likely that a cranioplasty patient may need to undergo further surgery at a later stage. In this context, a PMMA implant will usually be easy to detach, both at its border and the surface in contact with the dura, as it interacts little or not at all with the surrounding biological tissue, even after many years.

It is undisputed that the biological behaviour of a PHA prosthesis is different from that of PMMA implants. Indeed, the osteointegration of PHA prostheses increases exponentially over time and may be complete in as little as a year. Should further surgery need to be performed, this will make craniotomy necessary, as if the cranioplasty implant were normal skull tissue, even featuring a greater resistance to trepanation.

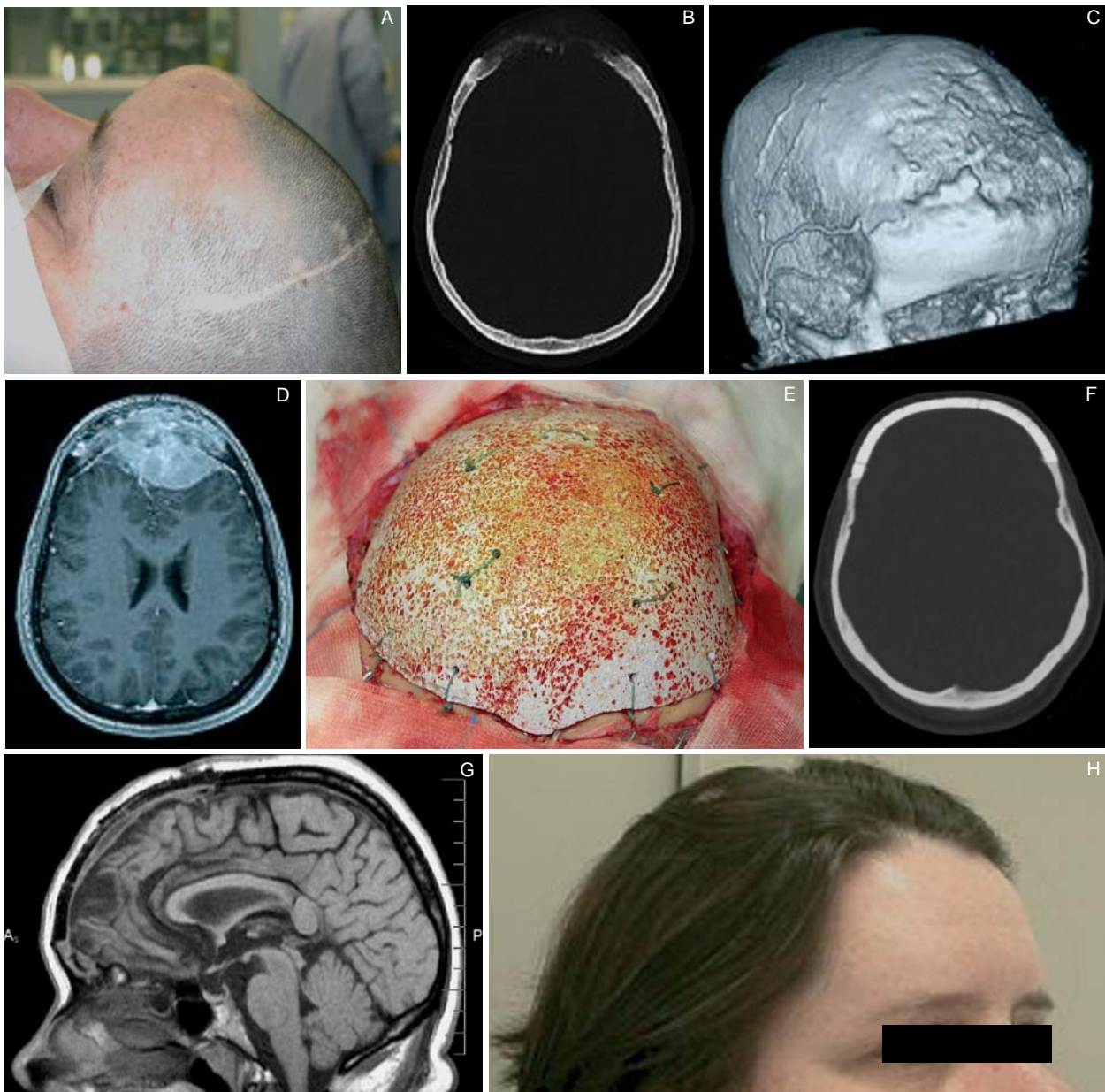
#### □ CONCLUSIONS

Neuroimaging is now used at practically every stage in the construction and fitting of a custom-made cranioplasty implant, particularly in demolition/reconstruction cases; the initial CT acquisitions of the patient's skull, the following 3D model in resin and the subsequent neuronavigation to create the implant housing all rely on neuroimaging. Currently, this computerized chain of events from prosthesis design to the surgery itself is indispensable if optimal results are to be achieved.

Although the precision furnished by the navigator is high, machine-related error does exist, particularly when superimposing the CT images of the skull model over the head MRI of the patient. To this is added any error in drilling, which may occur despite the use of the neuronavigator. Nevertheless, the positional inaccuracy (usually of the order of a few mm) is certainly lower than would be achieved if the demolition were performed in conjunction with a template of the prosthesis (like a sheet of dural substitute cutted to the proper shape or the prosthesis itself) and localization were guided by simple anatomical points, where positioning error can reach, and even exceed, a centimetre. Furthermore, extensive use of the neuronavigator during the surgical procedure can considerably reduce operating times, in that the craniectomy is per-



**Figure 20.** A natural complement to neuronavigator-assisted surgery is intraoperative CT (A). This is extremely useful as it consents to check the correct position of cranioplasty in real time (B).



**Figure 21.** A 45-year old female patient with atypical meningioma relapse at the forehead (A). Axial CT showing involvement and destruction of the bony plate (B). 3D rendering based on cranial CT images (C). Axial contrast-enhanced MRI (D). Custom-made PHA cranioplasty implant in situ after neuronavigator-assisted surgery. Note the extroflexion at the sagittal side of the implant (“jig-saw” technique) to prevent dislocation (E). Post-surgical follow-up at two years: axial cranial CT (F) and sagittal cranial MRI (G). Aesthetic outcome 1 year after neuro-navigator-assisted cranial demolition/reconstruction (H).

formed rapidly and precisely, without the need for continual checking of the moulded implant.

Given that the technology can assist the entire procedure, and that the neuronavigator is considered a valid tool in all neurosurgical units, except in extraordinary cases, single-sitting demolition/reconstruction surgery and neuronavigator-assisted positioning of cus-

tom-made cranioplasty implants should be routine practice. Indeed, the success of such a neuronavigator-guided procedure can be verified in during the operation itself by means of CT scans, which can be used to ascertain that the lesion has been removed correctly and the prosthesis has been accurately fitted while the patient is in the theatre (Figure 20). This is

particularly important when surgery takes place between the neuro- and splanchnocranium (orbital area, nasal root, zygomatic bones, etc.), where restoring symmetry is essential. In fact, CT not only consents morphological evaluation, but also linear and geometric measurements to be made in real time.

In our Centre, optimal results are made possible not only by the adoption of the procedure detailed above, but also by an intensive multidisciplinary effort, which, from a surgical perspective, involves the participation of plastic, maxillofacial and neurosurgery specialists<sup>(33)</sup> (Figure 21). Indeed, the cranioccephalic district is, by nature and definition, the province of various medical professionals, who, thanks to technological advances such as those described above, can collaborate to provide excellent functional and aesthetic outcomes in such cases.

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