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Short running head: Surgery of invasive cancers of the scalp

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ABSTRACT

Background: There is no universal management protocol concerning invasive malignant tumors of the scalp with bone and dura mater invasion. The aim of this study was to report and discuss our experience in the management of these forms of tumors.

Methods: We retrospectively reviewed all consecutive patients of microsurgical scalp reconstruction performed after resection of invasive cutaneous malignancies of the scalp, calvarium and dura mater from 2017 to 2019, at Pitié-Salpêtrière University Hospital (Paris, France).

Results: Five patients met inclusion criteria. There were 3 squamous cell carcinomas and 2 undifferentiated sarcomas. Mean age at surgery was 63.6 years. The sex ratio male/female was 4. Two received radiation prior to resection and 2 patients had a history of prior scalp tumor surgery. All the patients underwent craniectomy and the mean cranial defect size was 41cm^2. Cranioplasty was performed in one patient. Soft tissue coverage was provided by free tissue transfer of latissimus dorsi muscle in all patients. In 4 patients, split-thickness skin graft was performed in a second surgical stage few weeks later. There were no intraoperative complications and no complications into the donor site for the tissue transfer or the skin graft. Two patients had flap necrosis that healed after a new free flap of latissimus dorsi.

Conclusions: Wide resection with craniectomy, and reconstruction with microvascular free tissue transfer provides safe and reliable treatment of recalcitrant invasive scalp skin cancers. The surgical management of these complex patients is a challenge that must be conducted by trained, experienced and multidisciplinary teams.

KEYWORDS

craniofacial microsurgery,

cranioplasty,

cutaneous malignancy,

free tissue transfer,

microsurgical reconstruction,

neurosurgery.

INTRODUCTION

Few data are available in the literature concerning scalp invasive malignancies and their surgical care (excision and reconstruction after large and complex resection of calvarium). Tumor excision with scalp and bone invasion can be a surgical challenge due to the size and the invasiveness of the tumor. Likewise, calvaria reconstruction after excision can be also challenging and is generally performed using skin grafts or large flap depending on the defect size. However, there is no universal management protocol for these forms of tumors. When they are invasive, craniectomy and dura mater excision may be required to obtain full tumor excision, which exposes the patient to a risk of cerebrospinal fluid leak and infection. After these procedures, there is no consensus on the need of cranioplasty after microsurgical reconstruction of the skin.

Reconstruction scalp and skull defect resulting from tumor excision present most difficulties for the surgeon. Wide excision may include skin, periosteum, skull and dura mater, creating a complex wound. The use of radiation therapy and chemotherapy can compromise healing and scalp's vascularization. Flaps used for reconstruction should be durable to support adjuvant treatment. In 1972, free tissue transfer for reconstruction of large scalp defect was used for the first time, with an omentum flap to cover the defect [15]. Since then, other series have demonstrated the efficacy of this approach [16, 23]. The aim of the present study was to report and discuss our experience in the management of invasive malignant tumors of the scalp with bone and dura mater invasion.

PATIENTS AND METHODS

Patients recruitment

We retrospectively reviewed all consecutive patients of microsurgical scalp reconstruction performed after resection of invasive cutaneous malignancies of the scalp, calvarium and dura mater from February 2017 to July 2019, at Pitié-Salpêtrière University Hospital (Paris, France).

Presurgical evaluation included: complete general and neurological examination, brain MRI and CT-scan, body scanner and in some cases body positron emission tomography (PET). These data

were analyzed by a multidisciplinary team, including plastic surgeon, neurosurgeon, anesthetist, oncologist, radiotherapist, dermatologist and radiologist, to determine whether surgical treatment was indicated and whether a postoperative treatment would be required.

Classification of comorbidities and outcomes

Patient's data were collected through review of medical records. Current smoking was defined as smoking within 2 months of surgery. Hypertension and hyperlipidemia were defined by the use of antihypertensive and cholesterol-lowering drugs, respectively. Diabetes was defined by the use of oral hypoglycemic drugs or insulin. Immunosuppression was defined by use of immunosuppressive drugs or diagnosis known to cause an immunocompromised state. Patient's preoperative physical status was classified using the American Society of Anesthesiologists (ASA) score. Patients with a mild systemic disease were classified as ASA II. Patients with a systemic disease which is not incapacitating were classified as ASA III, and patients with an incapacitating systemic disease which is life-threatening were classified as ASA IV.

Measurement of skull defects were performed on postoperative CT-scans. Patients were carefully followed to ensure that no complications were missed. Cerebral spinal fluid (CSF) leak was defined by the presence of fluid collected from the operative site. Partial flap loss was defined as flap necrosis that resulted in subtotal loss of flap, while complete flap loss was defined as requiring total flap replacement.

***Standard Protocol Approvals, Registrations and Patient Consent*s**

The database is registered with the *Commission Nationale de l'Informatique et des Libertés* (n°. 2214386). In accordance with the ethical standards of our hospital's institutional review board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed for demographic, physiological and hospital-outcome data analyses because this observational study did not modify existing diagnostic or therapeutic strategies; however, patients were informed of their inclusion in the study. The manuscript was prepared in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement.

RESULTS

Patient characteristics

We found 5 patients who underwent resection followed by reconstruction surgery for invasive malignant tumors of the scalp extending into the calvarium and the dura mater. Mean age at surgery was 63.6 ± 9.2 years (range 35-84). The sex ratio male/female was 4. Preoperative patient comorbidities are summarized in Table 1. The mean follow-up period was 19 (range 7-36) months.

Tumor characteristics and surgical management

Of the 5 patients included in the study, 3 had stage IVA squamous cell carcinomas and 2 had sarcomas (one grade III undifferentiated sarcoma and one low-grade myofibroblastic sarcoma). The 3 patients with squamous cell carcinomas presented both clinical and histological poor prognostic factors according to the National Comprehensive Cancer Network (NCCN, USA) classification [18]. Two patients were treated by radiation therapy prior to resection (#1 and #2) and 2 patients had a history of prior scalp tumor surgery (#1 and #5). None of the patients had adjuvant lymph node excision.

Two patients had active scalp infections at the time of presentation: one had methicillin-resistant Staphylococcus aureus (MRSA) plus *Proteus mirabilis* plus *Enterococcus Faecalis* extra- and subdural empyema with skull necrosis that required surgical evacuation and intravenous antibiotics prior to reconstruction surgery (#1, Fig. 1 a, b), and the second one had methicillin-susceptible *Staphylococcus aureus* superficial infection treated with oral antibiotics (#4, Fig. 2 a-c). Three patients had tumor-related cerebral venous thrombosis before surgery: two had partial superior sagittal sinus thrombosis (#2 and #4, Fig. 2 a) and had one cortical vein thrombosis (#1, Fig. 1 A) that needed postoperative anticoagulation therapy.

All patients underwent wide scalp resection, craniectomy and dural electrocoagulation (Table 2). The mean cranial defect size was 41 cm^2 (3.4 - 155). The 3 patients who had a dural resection required primary dural repair. Cranioplasty was performed on the same surgical stage in one patient (#2, Fig. 3 c). Soft tissue coverage was provided by free tissue transfer of latissimus dorsi muscle in all

patients (#1, Fig. 1 c, e; #2, Fig. 3 d; #3, Fig. 4 e). The recipient vessels were the superficial temporal artery and vein in all patients. Mean surgical duration was 7.3 (range 5 - 10.5) hours. Mean intraoperative blood loss was 780 (range 400 - 1500) ml. In 4 patients (80%) split-thickness skin graft was performed in a second surgical stage few weeks later (Fig. 1 d, e; Fig. 3 d; Fig. 4 e).

Postoperative management

In the postoperative period, all patients underwent CT-scan to detect potential early intracranial bleeding and then received subcutaneous heparin. Four patients had been staying for only 24 hours in the intensive care unit, and one patient had been staying for 7 days (#1). The median total days of hospitalization was 9 (range 8 – 35) days. Four patients were discharged home and 1 was discharged to a rehabilitation center before returning home.

Patients operated on for squamous cell carcinomas did not receive any adjuvant treatment, while adjuvant radiotherapy has been performed in patients with sarcoma. A patient with systemic metastases of sarcoma (#3) received additional chemotherapy (adriamycin 60mg/m^2). Of the 5 patients, 1 patient who experienced an early local tumor recurrence died 7 months after surgery (#4), and 1 patient died within 10 months of surgery because of multiple systemic metastases (#3). The remaining 3 patients had no recurrence at 12, 34 and 36 months after the surgery, respectively.

Complications

There were no intraoperative complications and no complications into the donor site for the tissue transfer or the skin graft. All free tissue transfers achieved 100% soft tissue coverage. Postoperative complications included one CSF leak that required lumbar punctures (#2). Two patients had flap necrosis due to arterial thrombosis (#3 and #5) 7 and 3 days after surgery respectively, that healed after a surgical management consisting of a new free flap of latissimus dorsi. One patient experienced flap dehiscence (#4) which was treated using topical skin care. There were no complications in the 4 patients who had skin grafts.

DISCUSSION

The common cutaneous neoplasms of the scalp (squamous cell carcinoma, basal cell carcinoma, and malignant melanoma) are usually successfully treated with soft tissue excision, and scalp reconstruction using primary repair, local flaps or skin grafting [2, 17]. All of our patients showed invasion of their cutaneous malignancies into the cranium. This was evidenced preoperatively on imaging and confirmed intraoperatively. These patients were first recused by other local or regional hospitals because of the risk of postoperative complications and then referred to our tertiary center. Reconstruction was considerably challenging in these patients given their tumor size, and because the quality of the surrounding tissue was compromised by prior surgery, radiation or infection. Our management of these cutaneous malignancies of the scalp with deep invasion was therefore guided by the balance between obtaining clear surgical margins while avoiding neurological complications. A multidisciplinary approach has been successful in achieving complete surgical excision and immediate single-stage soft tissue reconstruction.

Post-operative defect was covered by free tissue transfer of latissimus dorsi muscle with split-thickness skin graft. Other flap techniques such as rectus abdominis muscle or antero-lateral thigh were also eligible. However, free flaps are optimal for reconstruction of large skin defects [9]. In cases which require postoperative irradiation, free flap might be more reliable than local pedicle flaps. Furthermore, the skin graft at the donor site may not tolerate postoperative irradiation [6, 8, 16]. Latissimus dorsi muscle is a large, broad and flat muscle providing stable soft tissue coverage, particularly if additional scalp needs to be resected in order to remove substrate for potential tumor recurrence [20]. The thoracodorsal artery and the thoracodorsal vein collected with this flap are of ideal caliber and length to perform the microsurgical vascular anastomosis [19]. The latissimus dorsi muscle flap also has the advantage of mimicking native scalp thickness and contour. Although secondary to the control of the malignancy, the aesthetic result of the reconstruction is an important consideration. Free flaps achieve good aesthetic results both in non-hearing and hearing areas [13].

Complications after surgery for reconstruction of scalp and calvaria in skin cancers are frequent.[24] They are more frequent when skin cancer involves bone and dura mater, and

196 complications include CSF leak, sinus and cortical veins thrombosis, and neurological impairment.
197 Our patients had voluminous and invasive tumors, and had poor general health condition and serious
198 comorbidities, that can explain the high rate of flap necrosis. The two cases of flap loss requiring
199 revision surgery occurred in patients with poor general status and active smoking, the latter being a
200 well-known risk factor for complication after free flap tissue transfer.[3, 7, 22] Special attention
201 should therefore be paid to smoking patients in the postoperative period. We recommend a systematic
202 intervention for smoking cessation before the surgery.[4] Moreover, chronic use of corticosteroids
203 does not increase rates of wound complications, reoperation, or readmission. However, this population
204 of patients may be at increased risk for major bleedings requiring blood transfusion following free flap
205 reconstruction.[25] Superior longitudinal sinus thrombosis can occur especially in patients with
206 tumoral involvement of the dura mater and requires pre- and/or postoperative anticoagulation therapy.
207 Finally, patients whose surgery is delayed have a poor prognosis, suggesting that early detection and
208 treatment are crucial.[1]

209 Despite flap loss in two of our patients, we obtained local healing after surgical revision. The
210 three other patients are currently in remission. Given the severity of the initial clinical presentation,
211 these outcomes can be considered as good. Indeed, oncological and esthetical benefits were major in
212 patients with no other therapeutic resources. Our experienced, shared by other teams, with these
213 advanced lesions is that even when resection is likely to be incomplete because of either sagittal sinus
214 involvement or the magnitude of the lesion, palliative resection and reconstruction are worth
215 considering [10, 14]. We therefore advocate for an aggressive and customized surgical management
216 involving multidisciplinary collaboration and strategic thinking.

217 For patients with large skull defects, the indications for cranioplasty are both functional, in
218 terms of cerebral protection, and aesthetic, to maintain the contour of the calvarium. Nevertheless,
219 performing a cranioplasty during the immediate reconstruction remains controversial, because it
220 increases the risk of postoperative infection while it does not require a second surgery. In our series,
221 we performed immediate cranioplasty in only one patient who experienced no serious postoperative
222 adverse events. The other patients presented exophytic ulcerated tumors with concomitant
223 contamination or infection, that are contraindications for subsequent cranioplasty. In a study

evaluating alloplastic cranioplasty, an infection rate of 40% was reported when calvarium was reconstructed with cranioplasty in the same surgical stage [5]. Several studies reported high complication rates (from 33 to 57%), when cranioplasty was performed during the immediate reconstruction, which required in most cases the removal of the prothesis [1, 3, 21]. However, these studies were not exclusively on patients with cranial defects due to resection of malignant tumors. Regardless of this, the higher complication rates reported in all studies about concomitant cranioplasty and scalp reconstruction have to be considered with caution. Several factors appeared to be important in these complications: the presence of residual devascularized or infected bone after excision, inadequate coverage of the cranioplasty with well-vascularized free tissue, and the nature of the material used for the cranioplasty [11, 14]. Preoperative and intraoperative recognition of the extent of the bony abnormality appears therefore fundamental to guide both tumor resection and cranioplasty. Cho et al. reported 11 cases of reconstruction without cranioplasty for recalcitrant invasive skin cancer of the scalp and proposed to avoid cranioplasty during the immediate reconstruction [5]. Moreover, in the Bethesda Cranial Facial Reconstruction Protocol delayed skull reconstruction resulted in a lower complication rate than previously described [12]. This approach is based on the two major advantages theoretically provided if cranioplasty is avoided at first excision. First, as seen in patients without dural repair, having a vascularized graft immediately on the dura mater can limit the creation of epidural fluid collections [12]. The second advantage of delaying cranioplasty is evidenced in patients who underwent dural repair using xenograft material and in whom the contact with a well-vascularized flap seemed to aid in healing and decreased CSF leaks [5]. Finally, although experience with cranioplasty is limited, the use of titanium mesh satisfies our requirements of a malleable but sturdy implant, which can be fixed rigidly.

CONCLUSION

Wide resection with craniectomy, and reconstruction with free tissue transfer with or without cranioplasty provide safe and reliable treatment for invasive malignant tumors of the scalp. The free tissue transfer of latissimus dorsi muscle is the mainstay to cover complex scalp defects and tolerate radiation. The place of cranioplasty during the immediate reconstruction remains controversial and is still debated. Anyhow, the surgical management of these complex patients is a challenge that must be conducted by trained, experienced and multidisciplinary teams comprising neurosurgeons, plastic surgeons and dedicated anesthetists.

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Conflict of Interest:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

Informed consent was obtained from all individual participants included in the study.

Patient photographic authorization:

All patients included in this study had given photographic authorization.

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FIGURE LEGENDS

Fig. 1 (patient #1)

A 35-year-old man with a history of sarcoma (diagnosed in 2000 in Algeria with 5 resection surgeries between 2000 and 2017), arrived in France in July 2017. He presented a wide skin, bone and dura mater damage (**a and b**) with a left extra and subdural empyema (**a**). A three-stage surgical management was performed. First, skin and pericranium resection with craniectomy and empyema evacuation have been performed. Postoperatively, intravenous antibiotics and anticoagulation therapy were started to threat both empyema and a cortical vein thrombosis. The second surgical stage was the reconstruction of cranial and skin defects, using a free flap of latissimus dorsi muscle (**c**), performed one month after the first surgical time. Finally, two weeks after the second surgical stage, a skin graft (donor-site was anterior thigh face) allowed to cover the flap (**d**). Lateral view of follow-up at 6 weeks demonstrating stable soft tissue coverage (**e**).

Fig. 2 (patient #4)

A 70-year-old man who developed recurrent invasive squamous cell carcinoma after immunosuppression for living-related kidney transplant. Preoperative T1-weighted magnetic resonance imaging (**a**) and CT scan (**b**) show an ulcerated tumor with invasion through the scalp into the cranium with superior longitudinal sinus tumoral involvement (**c**). Scalp and calvarial defect after wide local excision (**d**). A large Surgicel sheet was used to repair the dural defect (**d**). The defect was then reconstructed by a latissimus dorsi muscle free flap.

Fig. 3 (patient #2)

A 61-year-old woman, with a long history of recurrent squamous cell carcinoma (diagnosed in 2012, treated by chemotherapy and radiotherapy between 2012 and 2015, with follow-up break between 2015 and 2017) arrived in September 2017. She presented a wide skin, bone and dura mater damage with tumor invasion of the superior longitudinal sinus (**a**). We performed skin (**b**), bone (**c**) and dura mater excision. In the same time, the defect was reconstructed with tailored titanium cranioplasty (**c**)

and free flap of latissimus dorsi muscle. The patient had a little CSF leak after surgery resolved with lumbar punctures. After three weeks, a skin graft (donor-site was antero-internal thigh face) allowed to cover the flap. View of follow-up after free latissimus dorsi muscle flap with split-thickness skin graft and postoperative radiation (**d**).

Fig. 4 (patient #3)

A 68-year-old man presented in February 2018 with a giant retro-auricular left undifferentiated sarcoma (diameter was 29 cm) involving skin, bone and dura mater (**a and b**). A preoperative embolization was performed to limit bleeding during the surgery. Two days after embolization, resection surgery was achieved (**c and d**). The defect was reconstructed in the same time with a free flap of latissimus dorsi muscle. Patient had a flap necrosis, one week after surgery, requiring a revision surgery with a new latissimus dorsi muscle free flap. This second surgery led to local healing (**e**).