19 Decision-Making in Orbital Mucormycosis: Conservative Versus Orbital Exenteration

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19.1 History of Orbital Exenteration

George Bartisch, a German physician, considered by many as the "father of modern ophthalmology," first reported orbital exenteration in 1583 [1]. The modern total orbital exenteration was reported by Golovine [2], and Coston and Small in 1981 simplified the technique [3]. Since then, several variations in the surgical procedure have been reported [4–14].

19.2 Changing Trends in Orbital Exenteration

Orbital exenteration is a potentially lifesaving yet mutilating surgery with permanent cosmetic blemish leaving the patients socially uncomfortable. It has been primarily reserved for extensive and infiltrative eyelid, ocular surface, adnexal, and intraocular malignancies with orbital extension and for advanced primary orbital malignancies where conservative treatment is not feasible [15–17]. Non-neoplastic conditions including ROCM constituted only a minority of indications in the previously published reports [4–14].

The COVID-19 pandemic led to an unfortunate rapid rise in the number of cases of ROCM undergoing orbital exenteration. It is possible that some of these patients could be conservatively managed without compromising on life salvage. On the contrary, inappropriate attempts at conservation may have implications on life salvage. Therefore, the treating clinicians need to understand the thin line between adopting conservative management and resorting to radical surgical interventions. The decision to conserve versus exenterate becomes logical if we were to follow a system of staging to evaluate the severity and triage the patients for management as appropriate.

19.3 Stages of ROCM

ROCM typically follows a sequence of evolution from the point of entry (nasal mucosa) to the point of proliferation (paranasal sinuses) with contiguous progression to involve the orbit and intracranial structures. There are non-contiguous routes of spread as well, though rare. Before outlining the management protocol, the clinicians must understand the stages of ROCM as described in Fig. 19.1 [18] which provides a logical

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N. Gupta, S. G. Honavar (eds.), *Rhino-Orbito-Cerebral Mucormycosis*,
https://doi.org/10.1007/978-981-16-9729-6_19

Proposed Staging of Rhino-Orbito-Cerebral Mucormycosis (ROCM)

Staging of Rhino-Orbito-Cererbral Mucormycosis	Symptoms	Signs	Primary Assessment	Confirmation of Diagnosis
Stage 1: Involvement of the nasal mucosa 1a: Limited to the middle turbinate 1b: Involvement of the inferior turbinate or ostium of the nasolacrimal duct 1c: Involvement of the nasal septum 1d: Bilateral nasal mucosal involvement	Nasal stuffiness, nasal discharge, foul smell, epistaxis	Foul-smelling sticky mucoid or black-tinged, or granular or haemorrhagic nasal discharge, nasal mucosal inflammation, erythema, violaceous or blue discoloration, pale ulcer, anaesthesia, ischmia, eschar	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Deep nasal swab or endoscopy-guided nasal swab or nasal mucosal biopsy for direct microscopy, culture and molecular diagnostics; nasal mucosal biopsy for rapid histopathology with special stains
Stage 2: Involvement of paranasal sinuses 2a: One sinus 2b: Two ipsilateral sinuses 2c: > Two ipsilateral sinuses and/or palate/oral cavity 2d: Bilateral paranasal sinus involvement or involvement of the zygoma or mandible	Symptoms in Stage 1 + facial pain,facial edema, dental pain, systemic symptoms (malaise, fever)	Signs in Stage 1 + unilateral or bilateral, localized or diffuse facial edema, edema localized over the sinuses, localized sinus tenderness	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 1 + sinus biopsy for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 3: Involvement of the orbit 3a: Nasolacrimal duct, medial orbit, vision unaffected 3b: Diffuse orbital involvement (>1 quadrant or >2 structures), vision unaffected 3c: Central retinal artery or ophthamic artery occlusion or superior ophthalmic vein thrombosis; involvement of the superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision 3d: Bilateral orbital involvement	Symptoms in Stage 1 and 2 + painin the eye, proptosis,ptosis, diplopia, loss of vision, infraorbital and facial V1 V2 nerve anesthesia	Signs in Stage 1 and 2 + conjunctival chemoses, isolated ocular motility restriction, ptosis, proptosis, infraorbital nerve anesthesia, central retinal artery occlusion, features of ophthalmic artery occlusion and superior ophthalmic vein thrombosis. V1 and V2 nerve anesthesia, and features of III, IV and VI nerve paisy indicating Orbital apex/superior orbital fissure involvement.	Diagnostic nasal endoscopy, Contrast-enhanced MRI (preferred) or CT-scan	Same as Stage 2 + orbital biopsy if indicated and if feasible (if the disease i predominantly orbital) for direct microscopy, culture and molecular diagnostics and rapid histopathology
Stage 4: Involvement of the CNS 4a: Focal or partial cavernous sinus involvement and/or involvement of the cribriform plate 4b: Diffuse cavernous sinus involvement and/or cavernous sinus thrombosis 4c: Involvement beyond the cavernous sinus, involvement of the skull base, internal carotid artery occlusion, brain infarction 4d: Multifocal or diffuse CNS disease	Symptoms in Stage 1 to 3 + bilateral proptosis paralysis, altered consciousness, focal seizures	Signs in Stage 1-3 (some features overlap with Stage 3) + V1 and V2 nerve anesthesia, ptosis, and features of III, IV and VI nerve palsy indicate cavernous sinus involvement. Bilaterality of these signs with contralateral orbital edema with no clinico-radiological evidence of paranasal sinus or orbital involvement on the contralateral side indicate cavernous sinus thrombosis. Hemiparesis, altered consciousness and focal seizures indicate brain invasion and infarction.	Diagnostic endoscopy, Contrast-enhanced CT Scan, MRI (preferred)	Same as Stage 3

Fig. 19.1 Stages of ROCM 18

representation of clinical severity. Stage 3 and stage 4 constitute orbital mucormycosis.

Optimal management of ROCM requires concerted action and rapid response by a multidisciplinary team of experts in diagnosis (radiology, microbiology, pathology, molecular biology), and medical (infectious disease, neurology, critical care), and surgical (otorhinolaryngology, ophthalmology, neurosurgery) care. Establishing a clinico-radiological assessment to ascertain the extent of disease and confirmation by direct microscopy are the primary steps that help plan the management approach.

19.4 Medical Management of ROCM

Comprehensive guidelines for the medical management of ROCM have been issued by the European Confederation of Medical Mycology (ECMM) and the Mycoses Study Group Education and Research Consortium (MSGERC) [19]. Immediate induction therapy includes intravenous liposomal Amphotericin B 5–10 mg/kg BW with strict metabolic control. In cases with contraindication to Amphotericin B due to impaired renal function, Isavuconazole IV 200 mg thrice a day on days 1–2, 200 mg once a day from day 3; or Posaconazole IV 300 mg twice a day on day 1, 300 mg once a day from day 2 must be given. Continuation of induction therapy with intravenous liposomal Amphotericin B 5–10 mg/kg BW is required for a minimum of 4 weeks, followed by step-down treatment (oral Isavuconazole 200 mg thrice a day on days 1–2, 200 mg once a day from day 3; or oral Posaconazole 300 mg twice a day on day 1, 300 mg once a day from day 2) for 3–6 months or a minimum of 6 weeks following clinico-radiological regression or stabilization [18]. Amphotericin B Deoxycholate or Amphotericin B Lipid Complex may be utilized in patients with good renal function.

19.5 Recommended Treatment Protocol for ROCM with Orbital Involvement

Aggressive debridement of the involved paranasal sinuses constitutes the primary surgical management in cases of ROCM [20]. It can be combined with conservative management of the orbital component, primary orbital exenteration, or deferred orbital surgical intervention. Stage-wise management of orbital mucormycosis has been depicted in Fig. 19.2.

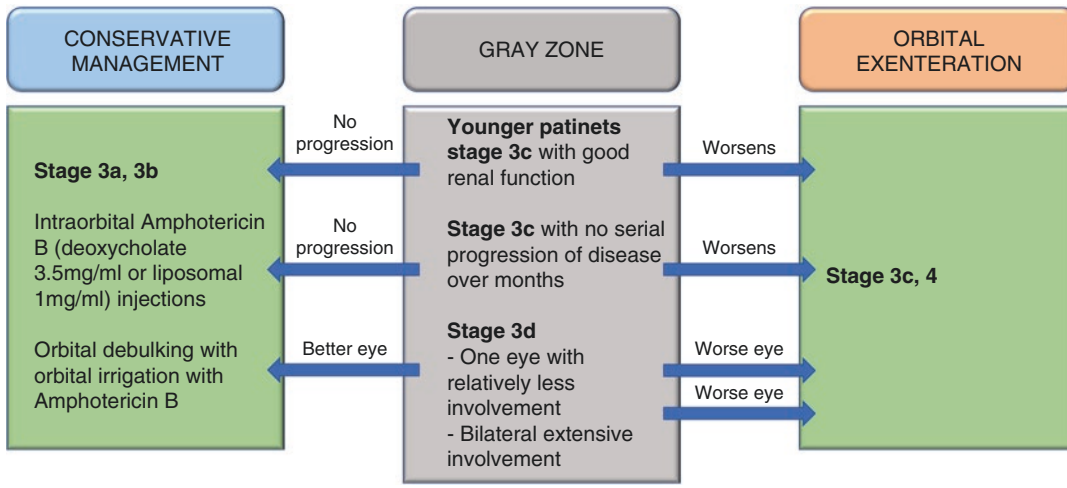

Fig. 19.2 Stage-wise management of orbital mucormycosis

19.6 Conservative Management in ROCM

There are clear indications for conservative management of the orbital disease as follows:

Stage 3a (involvement of the nasolacrimal duct and medial orbit, with unaffected vision): Stage 3a as shown in Fig. 19.3 describes localized orbital involvement, in which it is possible to treat the disease conservatively with medical management as described above along with intraorbital Amphotericin B injection (Deoxycholate Amphotericin B 3.5 mg/mL, Liposomal Amphotericin B 1 mg/mL) specifically to the area of involvement as confirmed by imaging. A series of 7 injections are provided daily or on alternate days depending on clinical severity and response, with clinico-radiological monitoring of response.

Stage 3b (diffuse orbital involvement, >1 quadrant or >2 structures, and unaffected vision): Stage 3b as seen in Fig. 19.4 was managed with intraorbital amphotericin B injections to the areas involved along with concomitant medical management and assessment of response clinico-radiologically and has responded remarkably well. In patients with a suboptimal response after 7 injections, limited orbital debulking is recommended, along with orbital irrigation with Amphotericin B 1 mg/mL.

Results of this approach are variable. Kohn and Helper have established that timely and accurate diagnosis of the extent of involvement attributes to favorable outcomes with conservative management thus avoiding mutilating surgeries and preserving visual acuity [22], and the same has been supported by Pelton et al. [23]. As per Sen et al., in the orbit, diffuse involvement predominated in 40% (674 of 1731) followed by involvement of the medial orbit in 27% (469). Orbital apex was involved in 21% (371) patients [21]. Kashkouli et al. have reported that out of the 34 eyes without exenteration, 41% progressed to complete loss of vision with a final vision survival of 25% in their series [24]. We believe that an accurate assessment of the extent of involve-

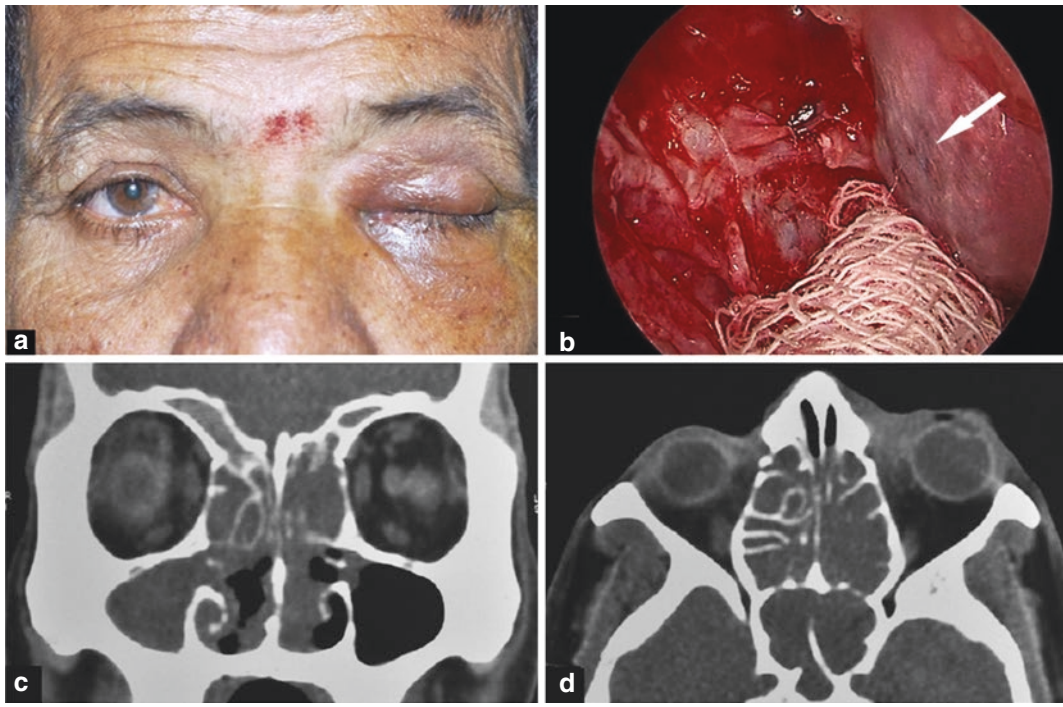

Fig. 19.3 Stage 3a ROCM (**a**) Clinical picture showing left periocular edema, ptosis and proptosis. (**b**) Endoscopy picture showing necrosed left periorbita (arrow). (**c**, **d**) Coronal and axial CT, respectively, showing left eye proptosis with diffuse bilateral paranasal sinus and left medial orbital involvement (Courtesy: Sen M et al. [21])

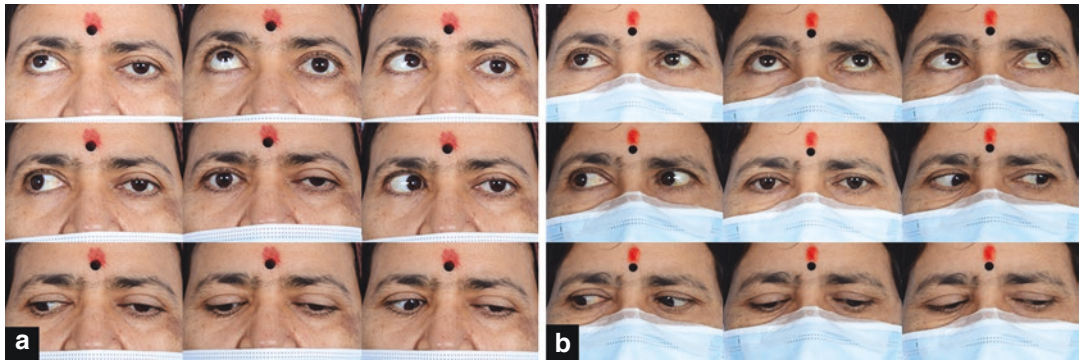

Fig. 19.4 Stage 3b ROCM: (**a**) A 56-year-old lady presented to us with left eye BCVA of light perception only, ptosis of 3 mm, restriction of movements in all directions with radiological evidence of involvement in the superomedial and inferomedial aspect. (**b**) After a series of seven injections of intraorbital Amphotericin B, she had complete resolution of symptoms and signs along with BCVA of 20/40 at the latest follow-up 5 months and interval decrease in the medial orbital involvement on MRI

ment and intraorbital Amphotericin B targeted to the area of involvement, early identification of poor responders and orbital exenteration in that subset are the keys to the success of this approach. Murthy et al. have reported 111 cases of ROCM treated conservatively with no recurrence for 3 months and not requiring orbital exenteration despite complete loss of vision (in five cases), thus avoiding mutilating surgeries [25].

19.7 Orbital Exenteration in ROCM

There are specific indications for orbital exenteration as follows:

Stage 3c (central retinal artery or ophthalmic artery occlusion or superior ophthalmic vein thrombosis; involvement of superior orbital fissure, inferior orbital fissure, orbital apex, loss of vision): This stage (Fig. 19.5) is a specific indication for orbital exenteration with continued medical management. Moorthy et al. have ascertained that an aggressive surgical approach reduces disease burden in these cases with irreversible blindness [26].

Stage 3d (bilateral orbital involvement): This stage requires a comparative analysis of orbital involvement (Fig. 19.6). Bilateral exenteration is not recommended and therefore, intraorbital Amphotericin B to the relatively better orbit along and exenteration of the more severely involved orbit is advised. Kashkouli et al. have reported four such patients in whom two cases were operated on for unilateral exenteration and another eye was left as blind eye and in the other two cases both eyes were left without any surgical intervention [24].

Stage 4 (central nervous system involvement): Sen et al. noted that in the CNS, cavernous sinus was most commonly involved in 53% (285 of 539), bilateral CNS involvement in 5% (133 of 2669) cases with cavernous sinus being the most common route of spread (70%, 299 of 430).

Even though in these cases (Fig. 19.7), the disease has progressed to involve the central nervous system, it has been observed that timely orbital exenteration results in faster recovery and halts the disease progression as is shown by Kashkouli et al. in their series of 79 eyes of 63 patients [24]. Jung et al. have stated that control of the underlying predisposing illness, prompt medical management, and aggressive surgical intervention decreases mortality [27].

19.8 Gray Zone

There are certain situations where cautious conservative measures can be employed:

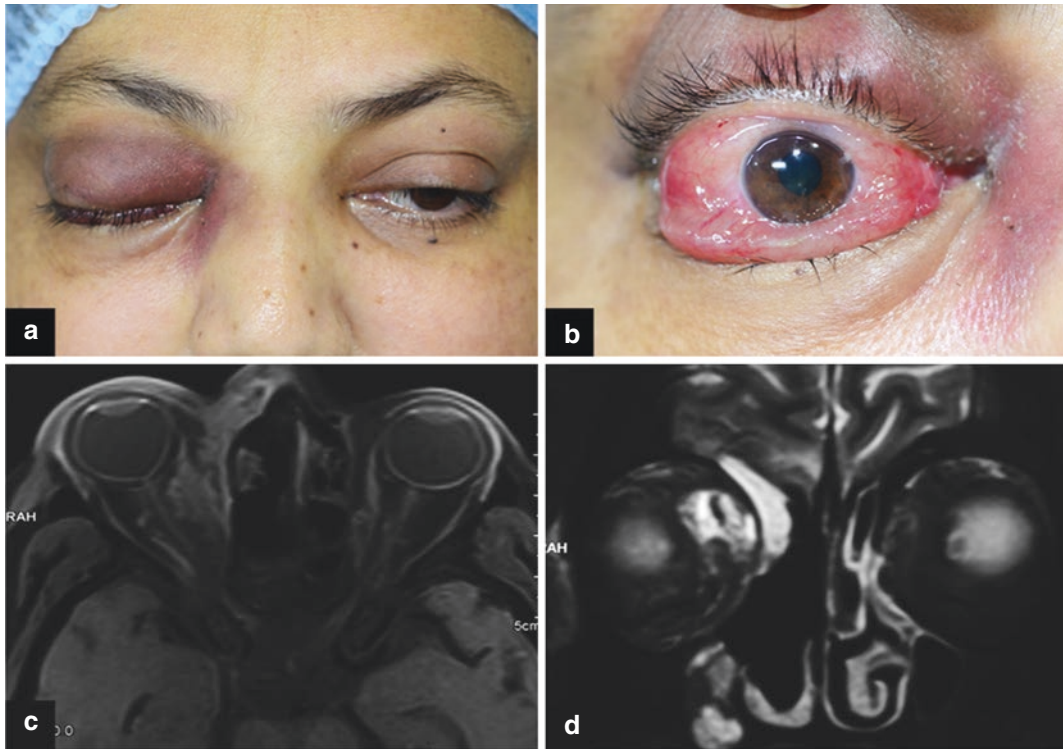

Fig. 19.5 Stage 3c ROCM (**a**) Clinical picture showing right eye ptosis, periocular edema, and ecchymosis. (**b**) Severe conjunctival congestion and chemosis. (**c**) Axial MRI (T1) of orbit and paranasal sinuses showing diffuse orbital involvement along with diffuse paranasal sinus involvement (s/p right paranasal sinus debridement and turbinectomy). (**d**) Coronal MRI (T2) showing unilateral diffuse right orbital involvement (Courtesy: Sen M et al. [21])

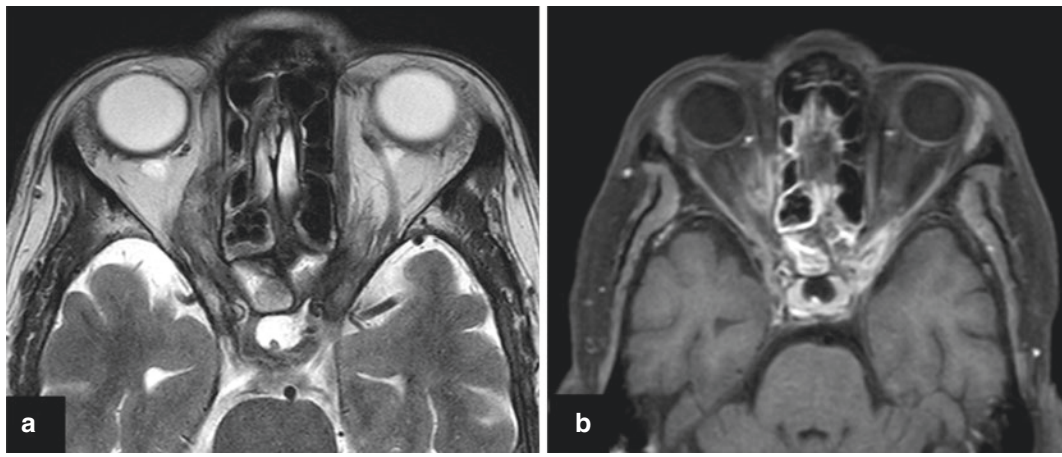

Fig. 19.6 Stage 3d ROCM (**a**) Axial MRI (T2) and (**b**) contrast enhanced (T1) of the orbit and paranasal sinuses showing bilateral orbital apical involvement, more extensive on the right side (Courtesy: Sen M et al. [21])

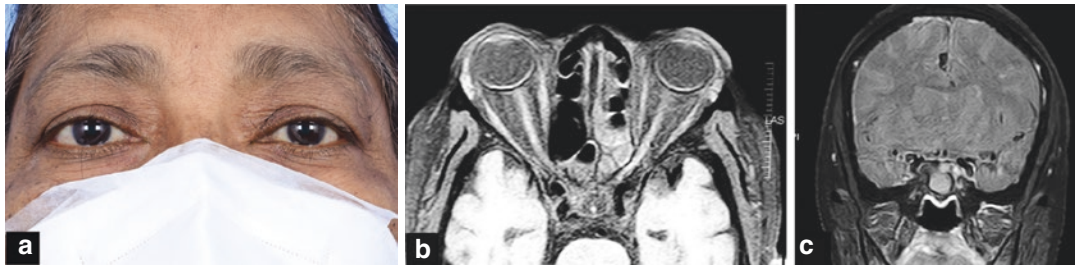

Fig. 19.7 Stage 4b ROCM (**a**) Clinical picture showing no significant ocular manifestation, however, (**b**) Axial MRI (T1) of the orbit, paranasal sinuses and brain showed diffuse paranasal sinus involvement along with (**c**) Coronal view (T1) showing extension into the cavernous sinus via the pterygopalatine fossa (Courtesy: Sen M et al. [21])

1. Younger patients with stage 3c or 3d with good renal function can be treated conservatively with intraorbital Amphotericin B, limited orbital debulking with close clinico-radiological monitoring, which on worsening can be triaged to orbital exenteration. Those improvement or stability can be continued on conservative treatment.
2. Young patients with bilateral orbital involvement (stage 3d) can be treated conservatively with intraorbital Amphotericin B, limited orbital debulking with close clinico-radiological monitoring.
3. Patients with extensive orbital invasion who cannot undergo immediate orbital exenteration due to coexistent uncontrolled comorbidities or continuing COVID-19-associated respiratory derangements.

Sen et al. reported that ROCM covers a wide range of age groups with a mean of 51.9 years (range, 12–88 years) [21], therefore, the decision about radical surgical interventions becomes difficult for the clinicians as well as for the families. It is imperative to weigh the advantages and disadvantages before making a decision (Fig. 19.8).

19.9 Prognosis

Hargrove et al. in an extensive literature review have stated that patients with ROCM with age >46 years, frontal sinus involvement, and fever had bleak chances of survival whereas patients treated with Amphotericin B had a better survival rate and that exenteration increases the likelihood of survival [28]. We have observed that out of 2826 cases assessed, the ocular outcome was available for 1838 patients, 16% (289) had orbital exenteration and in 84% (1549), the eye could be salvaged. With the protocol mentioned above, eye salvage was achieved in 100% (50 of 50) in stage 3a, 98% (81 of 83) in 3b, 83% (97 of 117) in 3c, 77% (10 of 13) in 3d, 71% (24 of 34) in 4a, 79% (11 of 14) in 4b, 82% (22 of 27) in 4c, and 67% (8 of 12) in 4d [21].

Multiple case series have reported a variable outcome including no effect to increased patients' survival [4, 23, 29, 30] to a significant decrease in survival rate [27, 28].

19.10 Challenges in Future

As the treatment entails a significant financial burden due to prolonged hospital stay, repeated radiological investigations, long recovery burden, maintenance therapy, and reconstructive surgeries, it leaves a major impact on the family. Psychological and cosmetic rehabilitation in patients undergoing orbital exenteration due to ROCM has to be handled delicately [31]. Dedicated counseling sessions are recommended for the ROCM survivors as they undergo multiple surgeries with long-term health-related issues within a short period [32].

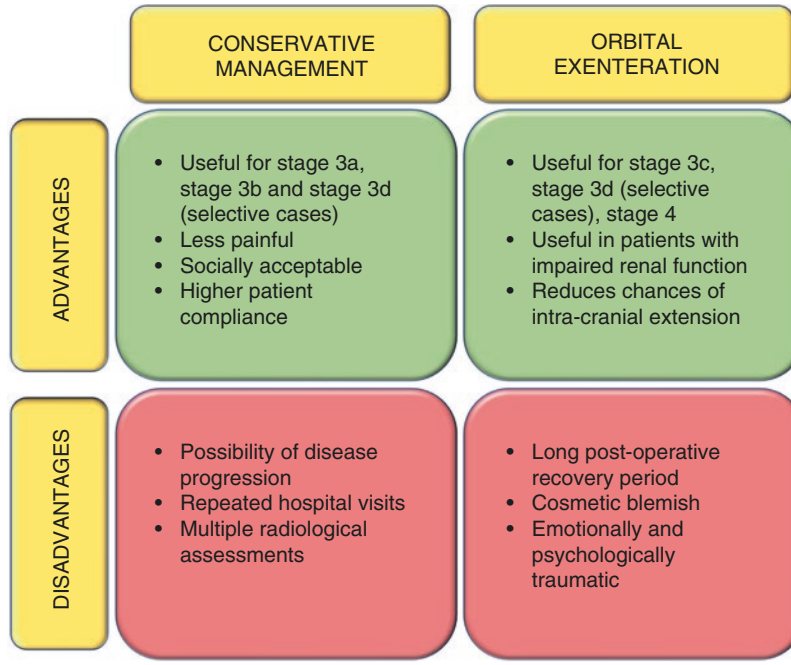

Fig. 19.8 Advantages and disadvantages of conservative treatment versus orbital exenteration

19.11 Conclusion

Among the cases of ROCM, a stage-based treatment protocol has been advocated which includes conservative management for stage 3a, stage 3b, and orbital exenteration for cases with stage 3c, stage 3d, and stage 4. There is, however, a gray zone, wherein for young patients with stage 3c and 3d ROCM, a cautious conservative approach can be considered. A balanced approach must be followed which comprises of a multidisciplinary team, accurate primary assessment of the extent of the disease, close monitoring of treatment response and disease progression by clinico-radiological assessment coupled with holistic consideration of psychological, social, and economical aspects helping in taking the decision for conservative treatment versus orbital exenteration.

References

1. Bartisch G. Ophthalmodouleia-das ist Augendienst. Matthes Sto¨ckel, Dresden 1583.
2. Golovine SS. Orbito-sinus exenteration. Ann Ocul. 1909;141:413–31.
3. Coston TO, Small RG. Orbital exenteration--simplified. Trans Am Ophthalmol Soc. 1981;79:136–52.
4. Bartley GB, Garrity JA, Waller RR, Henderson JW, Ilstrup DM. Orbital exenteration at the Mayo Clinic. 1967-1986. Ophthalmology. 1989;96(4):468–73.
5. Naquin HA. Exenteration of the orbit. AMA Arch Ophthalmol. 1954;51(6):850–62.
6. Ben Simon GJ, Schwarcz RM, Douglas R, Fiaschetti D, McCann JD, Goldberg RA. Orbital exenteration: one size does not fit all. Am J Ophthalmol. 2005;139(1):11–7.
7. Spaeth EB. Information learned from fifty years of orbital exenteration. Trans Ophthalmol Soc U K. 1971;91:611–34.
8. Rathbun JE, Beard C, Quickert MH. Evaluation of 48 cases of orbital exenteration. Am J Ophthalmol. 1971;72(1):191–9.
9. Nagendran ST, Lee NG, Fay A, Lefebvre DR, Sutula FC, Freitag SK. Orbital exenteration: the 10-year Massachusetts eye and ear infirmary experience. Orbit Amst Neth. 2016;35(4):199–206.
10. Rahman I, Cook AE, Leatherbarrow B. Orbital exenteration: a 13 year Manchester experience. Br J Ophthalmol. 2005;89(10):1335–40.
11. Mohr C, Esser J. Orbital exenteration: surgical and reconstructive strategies. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1997;235(5):288–95.
12. Levin PS, Dutton JJ. A 20-year series of orbital exenteration. Am J Ophthalmol. 1991;112(5):496–501.

13. Kasaee A, Eshraghi B, Nekoozadeh S, Ameli K, Sadeghi M, Jamshidian-Tehrani M. Orbital exenteration: a 23-year report. Korean J Ophthalmol KJO. 2019;33(4):366–70.
14. Shields JA, Shields CL, Demirci H, Honavar SG, Singh AD. Experience with eyelid-sparing orbital exenteration: the 2000 Tullos O. Coston lecture. Ophthal Plast Reconstr Surg. 2001;17(5):355–61.
15. Hoffman GR, Jefferson ND, Reid CBA, Eisenberg RL. Orbital exenteration to manage infiltrative sinonasal, orbital adnexal, and cutaneous malignancies provides acceptable survival outcomes: an institutional review, literature review, and meta-analysis. J Oral Maxillofac Surg. 2016;74(3):631–43.
16. Maheshwari R. Review of orbital exenteration from an eye care centre in Western India. Orbit Amst Neth. 2010;29(1):35–8.
17. Ackuaku-Dogbe E. Review of orbital exenterations in Korle-Bu teaching hospital. Ghana Med J. 2011;45(2):45–9.
18. Honavar SG. Code mucor: guidelines for the diagnosis, staging and management of rhino-orbito-cerebral mucormycosis in the setting of COVID-19. Indian J Ophthalmol. 2021;69(6):1361–5.
19. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):e405–21.
20. Sundaram N, Bhende T, Yashwant R, Jadhav S, Jain A. A review on outbreak of Mucormycosis in the COVID-19 patients. Indian J Ophthalmol. 2021;69(12):3728–33.
21. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India – collaborative OPAI-IJO study on mucormycosis in COVID-19 (COSMIC), report 1. Indian J Ophthalmol. 2021;69(7):1670–92.
22. Kohn R, Hepler R. Management of limited rhino-orbital mucormycosis without exenteration. Ophthalmology. 1985;92(10):1440–4.
23. Pelton RW, Peterson EA, Patel BC, Davis K. Successful treatment of rhino-orbital mucormycosis without exenteration: the use of multiple treatment modalities. Ophthal Plast Reconstr Surg. 2001;17(1):62–6.
24. Kashkouli MB, Abdolalizadeh P, Oghazian M, Hadi Y, Karimi N, Ghazizadeh M. Outcomes and factors affecting them in patients with rhino-orbito-cerebral mucormycosis. Br J Ophthalmol. 2019;103(10):1460–5.
25. Murthy R, Bagchi A, Gote YS. Role of medial orbital wall decompression in rhino-orbital mucormycosis management. Indian J Ophthalmol. 2021;69(12):3795–6.
26. Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, et al. SARS-CoV-2, uncontrolled diabetes and corticosteroids-an unholy trinity in invasive fungal infections of the maxillofacial region? A retrospective, multi-centric analysis. J Maxillofac Oral Surg. 2021;6:1–8.
27. Jung S-H, Kim SW, Park CS, Song CE, Cho JH, Lee JH, et al. Rhinocerebral Mucormycosis: consideration of prognostic factors and treatment modality. Auris Nasus Larynx. 2009;36(3):274–9.
28. Hargrove RN, Wesley RE, Klippenstein KA, Fleming JC, Haik BG. Indications for orbital exenteration in mucormycosis. Ophthal Plast Reconstr Surg. 2006;22(4):286–91.
29. Peterson KL, Wang M, Canalis RF, Abemayor E. Rhinocerebral mucormycosis: evolution of the disease and treatment options. Laryngoscope. 1997;107(7):855–62.
30. Ketenci I, Unlü Y, Kaya H, Somdaş MA, Kontaş O, Oztürk M, et al. Rhinocerebral mucormycosis: experience in 14 patients. J Laryngol Otol. 2011;125(8):e3.
31. Ackuaku-Dogbe EM, Biritwum RB, Briamah ZI. Psycho-social challenges of patients following orbital exenteration. East Afr Med J. 2012;89(12):385–9.
32. Sikka K, Goel G, Sharma N, Thakar A. Initial and ongoing challenged with COVID-19 associated Mucormycosis. Indian J Ophthalmol. 2021;69(12):3391–3.