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Case Report

A Case of Radiation-Induced Osteosarcoma with *RB1* Gene Alteration Treated by Skull Base Surgery and Craniofacial Reconstruction

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A 35-year-old female presented with headache, photophobia and developed sudden loss of vision after having undergone right-side ophthalmectomy and radiochemotherapy for retinoblastoma in infancy. A neoplastic lesion was found in the left middle cranial fossa and was surgically removed. The diagnosis was radiation-induced osteosarcoma with *RB1* gene alteration. Although she received chemotherapy for the residual tumor, it progressed 17 months later. Maximal surgical resection with craniofacial reconstruction was required. We utilized two three-dimensional models for surgical planning. She was discharged without neurological deficits other than loss of light perception subsequent to left ophthalmectomy. In cases where retinoblastoma is treated with radiotherapy, long-term follow-up is necessary to monitor for radiation-induced tumor development.

Key words: bone model, skull base surgery, radiation-induced osteosarcoma, *RB1* gene alteration

Radiation therapy has been used in cancer treatment for more than 100 years and has shown therapeutic benefits for malignancy. However, late side effects, including secondary neoplasia, can be a severe problem for long-term survivors. According to the United States National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database, the incidence of secondary neoplasia, including radiation-induced second malignancies (RISMs), has doubled over the past three decades [1]. The diagnostic criteria for RISMs have been modified over time from Cahan's original criteria [2]. Currently, for a tumor to be diagnosed as an RISM, (a) it must occur within the previously irradiated field, (b) there must be a sufficient latency period, such as several years, between the time of radiation and the time of tumor development, and (c) it must differ histologically from the primary disease.

Retinoblastoma is the most frequent primary ocular malignancy in the pediatric population, with an incidence of 1 per 15,000 to 20,000 live births worldwide [3,4]. Inactivation of the *RB1* tumor suppressor gene is related to the tumorigenesis of retinoblastoma, and the distribution of heritable versus non-heritable retinoblastoma cases is estimated to be 30-40% versus 60-70%, respectively [5]. Since *RB1* is a tumor suppressor gene, retinoblastoma survivors are at high risk for RISM. Indeed, RISM is the primary cause of death in retinoblastoma survivors [6,7]. Although bone sarcomas, including osteosarcoma, Ewing sarcoma, and chondrosarcoma, are the most common RISMs in reti-

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noblastoma, radiation-induced osteosarcoma is a rare tumor overall, comprising only 5.5% of all osteosarcomas and having an incidence of 0.01-0.03% in all irradiated patients [8]. Radiation-induced osteosarcoma is considered more aggressive than primary osteosarcoma in terms of both local recurrence rate and life expectancy [9-11] and requires multimodal therapy, including surgical resection and chemotherapy.

Here, we report a case of radiation-induced osteosarcoma of the left middle cranial fossa that developed approximately 35 years after radiotherapy for retinoblastoma. Multidisciplinary treatment was performed after careful preoperative examination using workstations and bone models.

Case Report

A 35-year-old female presented with headache and photophobia. The patient had been treated for bilateral retinoblastoma at 7 months of age with ophthalmectomy of the right eye, radiation (40 Gy for the left eye), and chemotherapy (vincristine + cyclophosphamide); left-side visual function was normal. Computed tomography (CT) and magnetic resonance imaging (MRI) showed a neoplastic lesion with calcification and bone destruction extending from the left middle cranial fossa to the left orbit (Fig. 1A, B). She developed rapid loss of vision in her left eye and underwent an emergent craniotomy. The tumor was partially resected at around 70%. Pathological analysis of tumor cells showed nuclear atypia and osteoid production, with a pathological diagnosis of osteosarcoma (Fig. 1C). Since her symptoms had worsened rapidly, she received postoperative chemotherapy for the residual tumor. She was treated with methotrexate, doxorubicin, and cisplatin chemotherapy and 6 cycles of high-dose ifosfamide for the remaining lesions, and the disease was well controlled. However, at 17 months after her initial surgery, MRI showed that the tumor was increasing in size, and the heterogenous contrast-enhanced tumor mass was mainly located on the anterior floor of the middle cranial fossa (Fig. 1D). CT scans revealed a predominantly osteoblastic expansive lesion of the left sphenoid ridge growing into the posterolateral orbit, compressing the

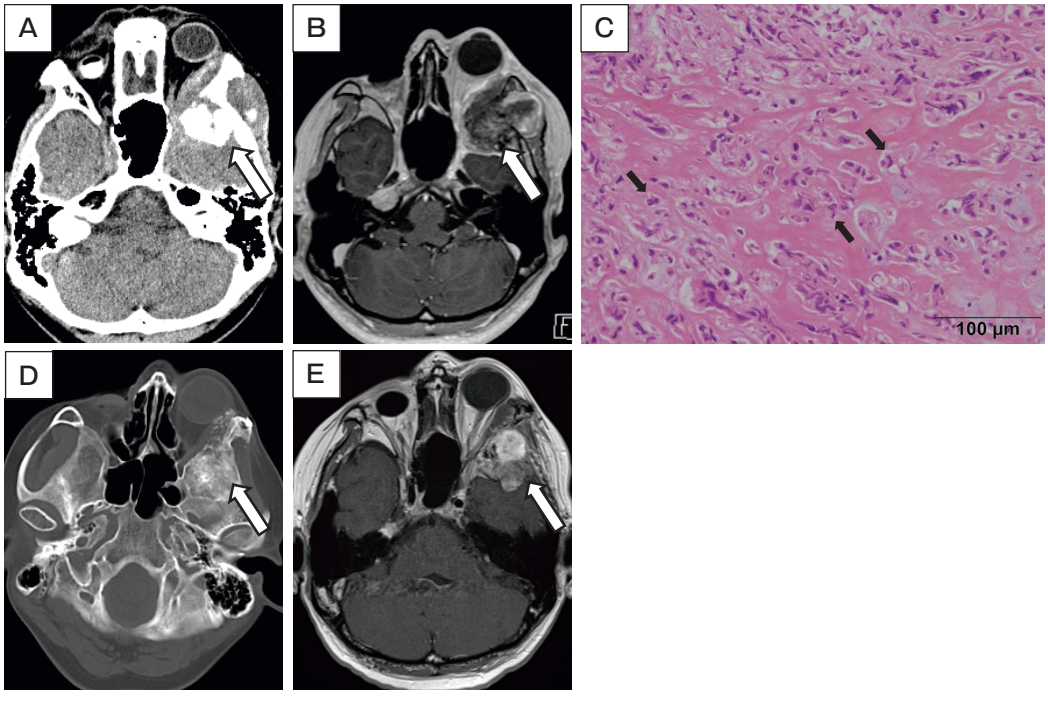

Fig. 1 Cranial imaging and pathological findings. Head CT and MRI prior to the initial surgery revealed a calcified and heterogenous enhanced tumor (A, B). Pathological analysis revealed that tumor cells with nuclear atypia produced osteoid (black arrow), and the pathological diagnosis was osteosarcoma. (C). Seventeen months later, head CT and MRI showed the progression of the tumor accompanied with an osteoblastic expansive lesion of the left sphenoid ridge growing into the posterolateral orbit, compressing the optic nerve, and invading the posterior wall of the maxillary sinus, pterygoid fossa, and middle cranial fossa (D, E).

optic nerve, and invading the posterior wall of the maxillary sinus, pterygoid fossa, and middle cranial fossa (Fig. 1E). At the time of tumor recurrence, her visual acuity was limited to light perception in the left eye, and her Karnofsky performance score (KPS) was 60.

Because the tumor was resistant to salvage chemotherapy (docetaxel, gemcitabine, and 1 course of high-dose ifosfamide), we planned extensive tumor resection and craniofacial reconstruction jointly with otolaryngologists and plastic surgeons. Prior to surgery, we utilized two three-dimensional (3D) models for surgical planning. First, we created a 3D fusion image from CT and MRI and visualized the tumor using a 3D image analysis system (Synapse Vincent Fujifilm Medical Inc., Tokyo, Japan) (Fig. 2A-C). Second, we prepared a patient-specific 3D skull base model and designed the resection line (Fig. 2D-G). The medial resection line connected the supraorbital notch and the foramen ovale through the medial aspect of the supraorbital fissure and foramen rotundum. The posterior resection line was set from the posterior part of the zygomatic arch and foramen ovale. As for the facial bone, we planned to resect it through the medial wall of the left orbit, left maxillary sinus, and infratemporal fossa. Removal of the contents of the left orbit, including the eyeball and part of the optic nerve, was included in the plan.

Prior to surgery, we embolized the left middle meningeal artery at the entry of the foramen spinosum to reduce intraoperative hemorrhage. On the day of surgery, we placed the bone model in a double-layered clean transparent plastic bag and brought it to the surgical field. Craniofacial resection was performed in accordance with the preoperative planning and the extradural part of the tumor was resected *en bloc*. Since the dura matter attached to the left sphenoid wing was thickened, we resected the dura matter to the furthest extent possible. In addition, the brain parenchyma in the left frontal and temporal lobe adjacent to this dura matter were also resected. The left eyeball and a portion of the optic nerve were carefully removed. After maximal tumor resection, craniofacial reconstructive surgery with a vascularized anterolateral thigh flap was performed (Fig. 3A-D). Postoperative CT and MRI showed the gross total resection of the tumor with margin (Fig. 3E-H).

On the first postoperative day, the blood flow of the

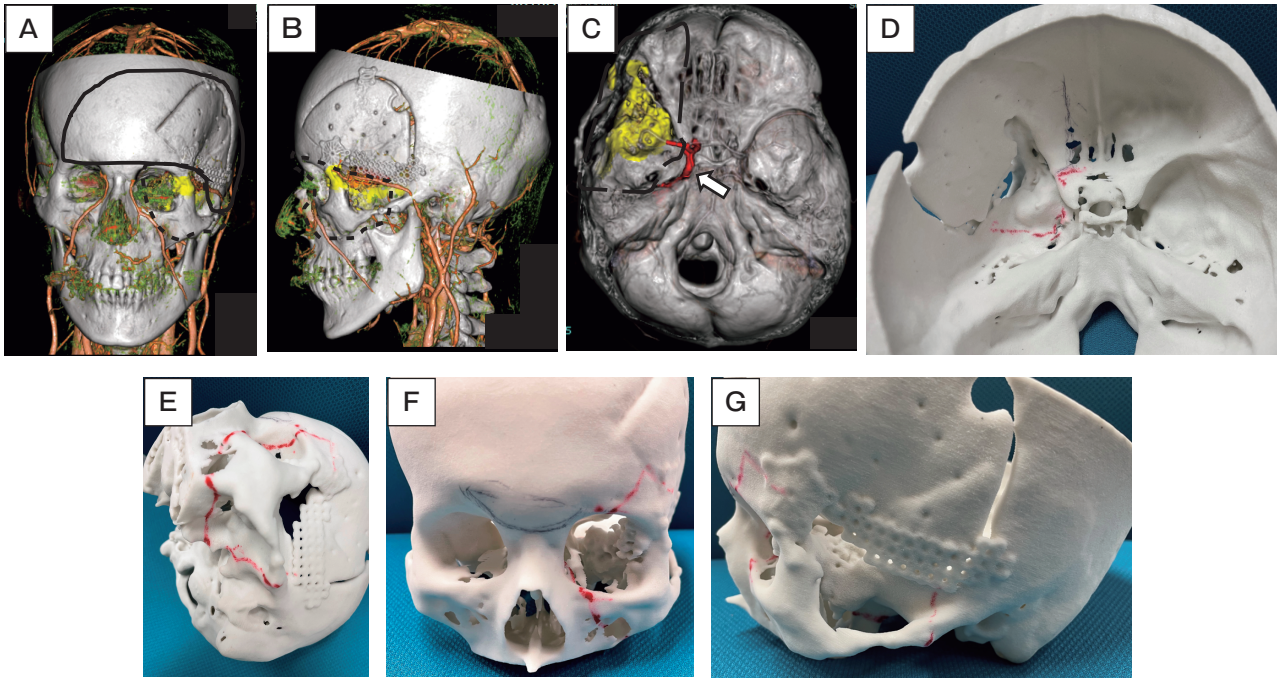

Fig. 2 Preoperative surgical planning utilizing two 3D models. A 3D fusion image was created using Synapse Vincent, with the tumor shown in yellow (A-C, **A**: frontal view, **B**: left lateral view, **C**: superior view). A 3D skull base model was also made, from which the resection line was designed (Fig. D-G, **D**: superior view, **E**: inferior view, **F**: frontal view, **G**: left lateral view). The white arrow indicates anterior circulation, including the internal carotid artery and middle cerebral artery.

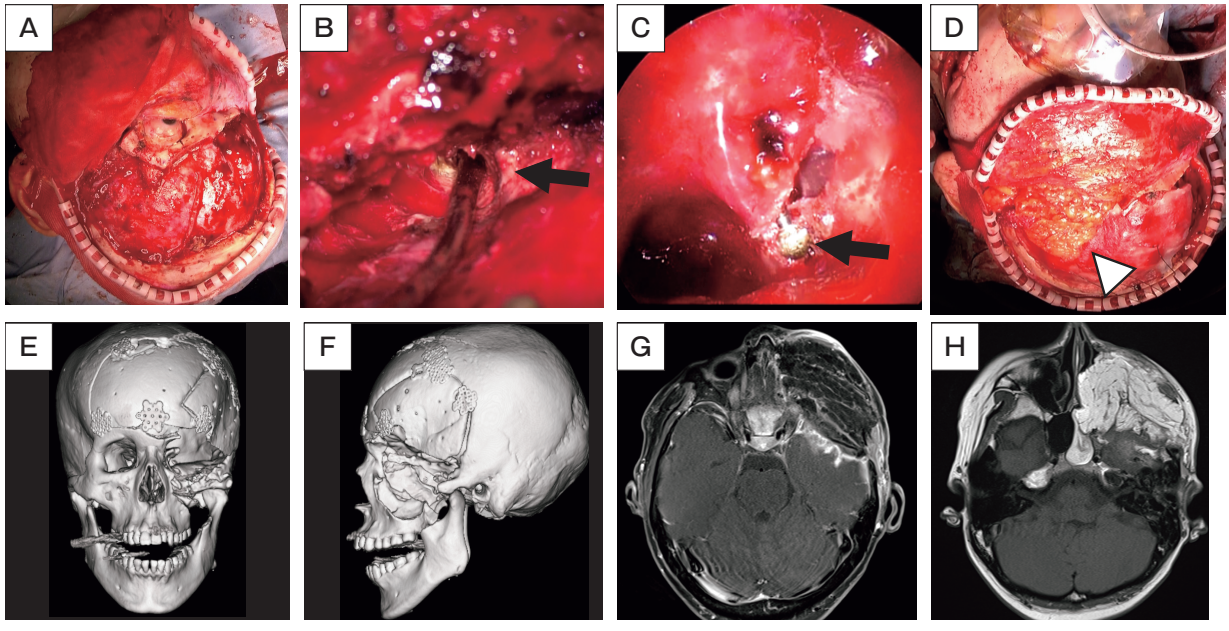

Fig. 3 Intraoperative findings and postoperative images. After preparing a skin flap, we approached the tumor through the anterior wall of the maxillary sinus and resected the tumor along the preoperatively designed line from the left orbit to the posterior wall of the maxillary sinus. Then, craniotomy was performed (**A**). The anterior and middle skull base were resected along the designed medial line from the supraorbital notch to the foramen ovale and posterior line. To connect the floor of the middle fossa and sphenoid sinus through the foramen rotundum, endoscopic assistance from the nasal cavity was useful (**B**: intracranial view; **C**: view from the sphenoid sinus). The black arrow indicates the diamond drill through the foramen rotundum. After gross total resection of the tumor, the vascularized flap (white arrow) from the right thigh was anastomosed to the facial artery and vein (**D**). Postoperative CT (**E**, **F**) and MRI show the gross total resection of the tumor (**G**). The resected cavity was filled with the fat pad and vascularized flap (**H**).

graft deteriorated and we performed re-anastomosis of the artery. In order to prevent cerebrospinal fluid (CSF) leakage, lumbar drainage was continued for 1 week after surgery. On neurological examination, immediately after surgery she had right hemiplegia and aphasia, which improved markedly within a few days. Her sense of smell was preserved. She was discharged home on postoperative day 17 at KPS 60. The pathological diagnosis was recurrence of osteosarcoma. At 15 months of follow-up, she has had no recurrence of the tumor.

Ethics approval. All procedures performed in this study were in accordance with the ethical standards of our institutional research committee (IRB#1911-023), which follows the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from the patient before treatment and prior to publication of this study.

Discussion

Retinoblastoma is a malignant tumor of childhood originating from retinoblasts. It is caused by "two-hit" inactivation of the *RB1* gene on chromosome 13, q14. Approximately 30% of the cases are bilateral while 70% are unilateral, but all bilateral cases and 10-15% of the unilateral cases totaling approximately 40% of all cases are hereditary, with germline alterations in the *RB1* gene inherited in an autosomal-dominant manner. Because the *RB1* gene is a tumor suppressor gene, hereditary retinoblastoma survivors are more likely to develop subsequent malignant neoplasms (SMN) because allelic mutations in one site of the *RB1* gene have already occurred in all cells. The SMN subtypes reported in retinoblastoma survivors are sarcoma (64%), carcinoma (13%), melanoma (8%), leukemia and lymphoma (4%), CNS tumor (4%), and other SMNs (7%). Of the SMN subtypes of sarcoma, 56% are bone sarcoma [7]. Four large cohort studies of long-term retinoblastoma survivors from the United Kingdom, United States, Netherlands, and Denmark have shown that hereditary retinoblastoma survivors have a much higher standardized incidence rate of SMN compared to

the general population, with an 11- to 20-fold higher incidence of tumors while non-hereditary retinoblastoma survivors do not have a higher incidence of tumors. The 40-year cumulative incidence of any SMN in the hereditary retinoblastoma survivor population was determined as 32.9% (95% confidence interval [CI]: 27-38.9) in the US and 28% (95% CI: 21.0-35.0) in the Netherlands, respectively [6, 12-14].

As for RISM, the long-term cumulative incidence of SMN is significantly higher in irradiated hereditary retinoblastoma survivors than in non-irradiated hereditary retinoblastoma survivors, by approximately threefold [15]. The strongest risk evidence is seen in sarcoma and melanoma, for which long-term surveillance is recommended [16-19]. The prognosis of radiation-induced osteosarcoma is very poor. The median progression-free survival and overall survival of skull base radiation-induced osteosarcoma are 9.5 and 41 months, respectively [9, 10]. Thus, multimodal treatment is required.

Skull base surgery requires the manipulation of deeply seated lesions surrounded by vital structures and a long operation time. As a result, the complication rate of skull base surgery is reported to be 33 to 54.7% [20-26], among which the postoperative spinal fluid leakage rate is reported to be 2 to 25% [27-29] and the meningitis rate is reported to be 1 to 10% [30]. In addition, the incidence of internal carotid artery injury, a major vascular injury, has been cited in 3 to 8% of reports [31, 32], although the number of reports is small and the actual percentage is expected to be higher. In order to reduce these complications, preoperative simulation and training are currently recommended. As attempts to apply 3D technology to human radiological data are increasing, surgical training and preoperative planning using a 3D model of the cranium made of artificial bone material are attracting attention [33, 34]. Surgical routes along the skull base are usually impeded by a variety of unpredictable blood vessels, bone shapes, and cranial nerve locations, so detailed individualized planning is needed to determine the best surgical approach. In addition, a realistic surgical simulation leads to surgeon confidence that the surgery will be performed smoothly and safely due to the so-called déjà vu effect [35-38]. In this case, in order to safely perform intraoperative procedures, the resection line was determined in preoperative meetings with all surgeons using 3D fusion images and 3D bone models. The tumor was resected as a gross total resection with a negative margin, with complete preservation of brain function.

In conclusion, we report a case of radiation-induced osteosarcoma after irradiation treatment for retinoblastoma in infancy. Although the former treatment for retinoblastoma had been external irradiation, to preserve the patient's vision, it is rarely practiced any more because of the risk of long-term complications, including RISM. Thus, it is important to maintain long-term follow-up for retinoblastoma patients who have been irradiated. After emergent surgery and relapse, the patient was successfully treated with carefully planned surgical resection and craniofacial reconstruction. In surgery for skull base malignancies, it is helpful to conduct comprehensive preoperative planning using bone models and other methods in collaboration with cooperating departments, thereby avoiding key neural and vascular structures.

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References

1. Morton LM, Onel K, Curtis RE, Hungate EA and Armstrong GT: The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. Am Soc Clin Oncol Educ Book (2014) e57–67.
2. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW and Coley BL: Sarcoma arising in irradiated bone: report of eleven cases. 1948. Cancer (1998) 82: 8–34.
3. Kivelä T: The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. Br J Ophthalmol (2009) 93: 1129–1131.
4. Dimaras H, Kimani K, Dimba EA, Gronsdahl P, White A, Chan HS and Gallie BL: Retinoblastoma. Lancet (2012) 379: 1436–1446.
5. Fujiwara T, Fujiwara M, Numoto K, Ogura K, Yoshida A, Yonemoto T, Suzuki S and Kawai A: Second primary osteosarcomas in patients with retinoblastoma. Jpn J Clin Oncol (2015) 45: 1139–1145.
6. Kleinerman RA, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, Li FP and Fraumeni JF, Jr.: Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: An extended follow-up. J Clin Oncol (2005) 23: 2272–2279.
7. Woo KI and Harbour JW: Review of 676 second primary tumors in patients with retinoblastoma: Association between age at onset and tumor type. Arch Ophthalmol (2010) 128: 865–870.
8. Goodman MA and McMaster JH: Primary osteosarcoma of the skull. Clin Orthop Relat Res (1976) 110–114.
9. Echchikhi Y, Loughlimi H, Touil A, Kebdani T and Benjaafar N: Radiation-induced osteosarcoma of the skull base after radiation therapy in a patient with nasopharyngeal carcinoma: A case report

and review of the literature. J Med Case Rep (2016) 10: 334.
10. Patel AJ, Rao VY, Fox BD, Suki D, Wildrick DM, Sawaya R and DeMonte F: Radiation-induced osteosarcomas of the calvarium and skull base. Cancer (2011) 117: 2120–2126.
11. Patel SG, Meyers P, Huvos AG, Wolden S, Singh B, Shaha AR, Boyle JO, Pfister D, Shah JP and Kraus DH: Improved outcomes in patients with osteogenic sarcoma of the head and neck. Cancer (2002) 95: 1495–1503.
12. Marees T, van Leeuwen FE, de Boer MR, Imhof SM, Ringens PJ and Moll AC: Cancer mortality in long-term survivors of retinoblastoma. Eur J Cancer (2009) 45: 3245–3253.
13. Gregersen PA, Olsen MH, Urbak SF, Funding M, Dalton SO, Overgaard J and Alsner J: Incidence and mortality of second primary cancers in Danish patients with retinoblastoma, 1943–2013. JAMA Netw Open (2020) 3: e2022126.
14. MacCarthy A, Bayne AM, Brownbill PA, Bunch KJ, Diggens NL, Draper GJ, Hawkins MM, Jenkinson HC, Kingston JE, Stiller CA, Vincent TJ and Murphy MF: Second and subsequent tumours among 1927 retinoblastoma patients diagnosed in Britain 1951–2004. Br J Cancer (2013) 108: 2455–2463.
15. Temming P, Arendt M, Viehmann A, Eisele L, Le Guin CH, Schündeln MM, Biewald E, Astrahantseff K, Wieland R, Bornfeld N, Sauerwein W, Eggert A, Jöckel KH and Lohmann DR: Incidence of second cancers after radiotherapy and systemic chemotherapy in heritable retinoblastoma survivors: A report from the German reference center. Pediatr Blood Cancer (2017) 64: 71–80.
16. Shinohara ET, DeWees T and Perkins SM: Subsequent malignancies and their effect on survival in patients with retinoblastoma. Pediatr Blood Cancer (2014) 61: 116–119.
17. Wong JR, Morton LM, Tucker MA, Abramson DH, Seddon JM, Sampson JN and Kleinerman RA: Risk of subsequent malignant neoplasms in long-term hereditary retinoblastoma survivors after chemotherapy and radiotherapy. J Clin Oncol (2014) 32: 3284–3290.
18. Tonorezos ES, Friedman DN, Barnea D, Bosscha MI, Chantada G, Dommering CJ, de Graaf P, Dunkel IJ, Fabius AWM, Francis JH, Greer MC, Kleinerman RA, Kors WA, Laughlin S, Moll AC, Morton LM, Temming P, Tucker MA, van Leeuwen FE, Walsh MF, Oeffinger KC and Abramson DH: Recommendations for Long-Term Follow-up of Adults with Heritable Retinoblastoma. Ophthalmology (2020) 127: 1549–1557.
19. Fabius AWM, van Hoefen Wijsard M, van Leeuwen FE and Moll AC: Subsequent Malignant Neoplasms in Retinoblastoma Survivors. Cancers (Basel) (2021) 13.
20. Bentz BG, Bilsky MH, Shah JP and Kraus D: Anterior skull base surgery for malignant tumors: A multivariate analysis of 27 years of experience. Head Neck (2003) 25: 515–520.
21. Clayman GL, DeMonte F, Jaffe DM, Schusterman MA, Weber RS, Miller MJ and Goepfert H: Outcome and complications of extended cranial-base resection requiring microvascular free-tissue transfer. Arch Otolaryngol Head Neck Surg (1995) 121: 1253–1257.
22. Dias FL, Sá GM, Kligerman J, Lopes HF, Wance JR, Paiva FP, Benévolo A and Freitas EQ: Complications of anterior craniofacial resection. Head Neck (1999) 21: 12–20.
23. Ganly I, Patel SG, Singh B, Kraus DH, Bridger PG, Cantu G, Cheesman A, De Sa G, Donald P, Fliss D, Gullane P, Janecka I, Kamata SE, Kowalski LP, Levine P, Medina LR, Pradhan S, Schramm V, Snyderman C, Wei WI and Shah JP: Complications of craniofacial resection for malignant tumors of the skull base: Report of an International Collaborative Study. Head Neck (2005) 27: 445–451.
24. Kraus DH, Shah JP, Arbit E, Galicich JH and Strong EW: Complications of craniofacial resection for tumors involving the anterior skull base. Head Neck (1994) 16: 307–312.
25. Shah JP, Kraus DH, Bilsky MH, Gutin PH, Harrison LH and Strong EW: Craniofacial resection for malignant tumors involving the anterior skull base. Arch Otolaryngol Head Neck Surg (1997) 123: 1312–1317.
26. Patel SG, Singh B, Polluri A, Bridger PG, Cantu G, Cheesman AD, deSa GM, Donald P, Fliss D, Gullane P, Janecka I, Kamata SE, Kowalski LP, Kraus DH, Levine PA, dos Santos LR, Pradhan S, Schramm V, Snyderman C, Wei WI and Shah JP: Craniofacial surgery for malignant skull base tumors: Report of an international collaborative study. Cancer (2003) 98: 1179–1187.
27. Donald PJ: Complications in skull base surgery for malignancy. Laryngoscope (1999) 109: 1959–1966.
28. Janecka IP, Sen C, Sekhar LN, Ramasastry S, Curtin HD, Barnes EL and D'Amico F: Cranial base surgery: Results in 183 patients. Otolaryngol Head Neck Surg (1994) 110: 539–546.
29. Nibu K, Sasaki T, Kawahara N, Sugasawa M, Nakatsuka T and Yamada A: Complications of craniofacial surgery for tumors involving the anterior cranial base. Neurosurgery (1998) 42: 455–462.
30. Kryzanski JT, Annino DJ, Gopal H and Heilman CB: Low complication rates of cranial and craniofacial approaches to midline anterior skull base lesions. Skull Base (2008) 18: 229–241.
31. Van Der Veken J, Simons M, Mulcahy MJ, Wurster C, Harding M and Van Velthoven V: The surgical management of intraoperative intracranial internal carotid artery injury in open skull base surgery-a systematic review. Neurosurg Rev (2021).
32. AlQahtani A, London NR, Jr., Castelnuovo P, Locatelli D, Stamm A, Cohen-Gadol AA, Elbosraty H, Casiano R, Morcos J, Pasquini E, Frank G, Mazzatenta D, Barkhoudarian G, Griffiths C, Kelly D, Georgalas C, Janakiram N, Nicolai P, Prevedello DM and Carrau RL: Assessment of Factors Associated With Internal Carotid Injury in Expanded Endoscopic Endonasal Skull Base Surgery. JAMA Otolaryngol Head Neck Surg (2020) 146: 364–372.
33. Mori K, Yamamoto T, Nakao Y and Esaki T: Development of artificial cranial base model with soft tissues for practical education: Technical note. Neurosurgery (2010) 66: 339–341.
34. Oishi M, Fukuda M, Yajima N, Yoshida K, Takahashi M, Hiraishi T, Takao T, Saito A and Fujii Y: Interactive presurgical simulation applying advanced 3D imaging and modeling techniques for skull base and deep tumors. J Neurosurg (2013) 119: 94–105.
35. Oishi M, Fukuda M, Ishida G, Saito A, Hiraishi T and Fujii Y: Prediction of the microsurgical window for skull-base tumors by advanced three-dimensional multi-fusion volumetric imaging. Neurol Med Chir (Tokyo) (2011) 51: 201–207.
36. Samii M and Gerganov VM: Surgery of extra-axial tumors of the cerebral base. Neurosurgery (2008) 62: 1153–1168.
37. Stadie AT, Kockro RA, Reisch R, Tropine A, Boor S, Stoeter P and Perneczky A: Virtual reality system for planning minimally invasive neurosurgery. Technical note. J Neurosurg (2008) 108: 382–394.
38. Oishi M, Fukuda M, Ishida G, Saito A, Hiraishi T and Fujii Y: Presurgical simulation with advanced 3-dimensional multifusion volumetric imaging in patients with skull base tumors. Neurosurgery (2011) 68: 188–199.