Surgical Pathology of the Skull Base: A 7-Year Experience

ABSTRACT—A significant diversity of tissue types interface at the base of the skull and contribute to the diagnostic challenges of skull base surgical pathology. Advances in surgical technique now permit biopsy and resection of lesions previously termed “inoperable.” Retrospective review was made of all pathology specimens from skull base surgeries performed at the University of California Davis Medical Center from 1990 to 1996. Surgical biopsies and resections were performed on 186 patients who had 33 distinctive diagnoses. Any preoperative biopsy or tissue from referring institutions was reviewed prior to skull base surgery. One hundred eighteen patients had benign lesions, the most frequent of which were pituitary adenoma (55) and acoustic neuroma (27). Other benign lesions included angiofibroma, meningioma, fibrous dysplasia, and paraganglioma. Sixty-eight patients had malignant tumors, 32 of which were squamous cell carcinoma. Other malignancies included salivary carcinomas, basal cell carcinoma, neuroblastoma, melanoma, and several sarcomas. Unexpected findings were two metastatic carcinomas and five inflammatory lesions. Nearly 1500 intraoperative consultations were performed to establish resection margins and less commonly to confirm the diagnosis. The discrepancy rate between the intraoperative and final diagnosis was 1.8%. Immunohistochemistry and/or electron microscopy was utilized in 44% of the specimens to confirm the diagnosis. Surgical pathology is an essential ingredient to a successful skull base surgery program. Pathologists are involved in both pre- and intraoperative decisions. The diversity of lesions that arise from the skull base often has overlapping histologies that require careful attention to morphology and the use of ancillary studies for accurate diagnosis. The need for frequent intraoperative interpretations contributes to the significant challenge for the surgical pathologist.

Lesions of the skull base present complex and often daunting challenges to surgeons and pathologists. The diversity of tissue types that interface at the base of skull is unparalleled in the human body and includes respiratory and squamous epithelia, submucosal minor salivary glands, specialized sensory tissues, neural tissues and their coverings, endocrine tissues, and a variety of connective tissues. These various tissue types give rise to numerous benign and malignant neoplasms of distinctive differentiation, morphology, and behavior.¹

The surgical pathologist often must consider a broad range of diagnostic possibilities including non-neoplastic entities and metastatic disease. The challenge of accurate diagnosis is frequently complicated by the urgency dictated by intraoperative consultation. The finding of clinically unexpected positive margins directly influenced the surgical resection to ensure total tumor removal. Our 7-year experience at the Center for Skull Base Surgery at the University of California Davis Medical Center (UCDMC) illustrates these phenomena.

METHODS

All surgical specimens obtained from patients treated at the Center for Skull Base Surgery at the UCDMC from 1990 to 1996 inclusive were reviewed by the skull base surgical pathologist (R.G.E.). These included biopsies and surgical resections as well as material that originated from outside institutions. Also reviewed were all tissues that were submitted for intraoperative consultation. The pathologic diagnoses were tabulated and related to skull base site: pituitary, temporal bone, infratemporal fossa, anterior cranial fossa, middle cranial fossa, and posterior cranial fossa (Tables 1, 2).

RESULTS

From January 1990 through December 1996, surgical biopsies and resections of the skull base were performed on 186 patients. Any preoperative biopsy or tissue from referring institutions was reviewed by the skull base pathologist prior to skull base surgery. These 186 patients presented 33 distinctive pathologic diagnoses. The majority of patients, 118 (63%), had benign lesions. Most of these were tumors originating from within the cranial cavity. The most common lesions were pituitary adenoma (55), schwannoma (30), and meningioma (14). Ninety percent of the schwannomas involved cranial nerve VIII (acoustic neuroma). The other schwannomas included two resected from the middle fossa and one from the infratemporal fossa. The 14 meningiomas were distributed in the anterior (4), middle (4), infratemporal (2) and posterior fossae (2), and temporal bone (2). Another group of neoplasms includes those "benign" lesions that often have an aggressive course. These were inverting papilloma (3), paraganglioma (3), chordoma (2), angiofibroma (1), and hemangiopericytoma (1). Non-neoplastic benign conditions included mucocoele in the frontal sinus–anterior fossa region, arthritic pannus of the upper cervical vertebrae, epidermoid cyst of the temporal bone, inflammatory pseudotumor of the infratemporal fossa, fibrous

dysplasia in the anterior fossa, and a solitary pituitary cyst.

Sixty-eight patients had malignant tumors, 32 (46%) of which were squamous cell carcinomas originating from the upper respiratory tract, skin of the scalp and face, and external auditory canal. Salivary carcinomas included four adenoid cystic carcinomas arising from the ethmoid sinuses and two parotid tumors: one mucoepidermoid carcinoma and one carcinoma ex pleomorphic adenoma, both of which involved the infratemporal fossa. All five of the basal cell carcinomas arising from auricular and facial skin had a sclerosing or "morphoeaform" histology.

Primary malignancies of the sinonasal tract included five olfactory neuroblastomas, four of the highly aggressive sinonasal undifferentiated carcinoma, three sinonasal mucosal melanomas, two diffuse, large B-cell lymphomas, and one nasopharyngeal carcinoma. A variety of soft tissue sarcomas was resected from the anterior, middle, and infratemporal fossae, which included three malignant peripheral nerve sheath tumors and one each of malignant fibrous histiocytoma, dermatofibrosarcoma protuberans, alveolar rhabdomyosarcoma, leiomyosarcoma, and chondrosarcoma. Two patients with clinically silent urinary tract malignancies presented with symptoms referable to the skull base. The two metastatic carcinomas included a renal cell carcinoma in the petrous portion of the temporal bone and a prostatic adenocarcinoma in the sphenoid sinus.

Nearly 1500 intraoperative consultations were performed, including frozen sections and touch preparations. The majority of these was requested to determine the margins of resection. A discrepancy between the intraoperative and final diagnosis was found in 28 specimens from 18 patients. The specimen error rate was 1.8%.

Immunohistochemistry (IHC) was utilized in 82 (44%) cases to confirm the diagnosis. The majority (93%) of pituitary adenomas were phenotyped using antibodies against the major pituitary hormones. IHC was significantly useful in the differential diagnosis of the small round cell tumors such as olfactory neuroblastoma, lymphoma, and alveolar rhabdomyosarcoma and in the poorly differentiated malignancies such as sinonasal undifferentiated carcinoma and melanoma. Electron microscopy was performed on 55 (29%) patient specimens and was particularly useful in the differential diagnosis of poorly differentiated malignancies.

Table 1. Skull Base Surgery Cases, 1990–1996, Center for Skull Base Surgery, University of California Davis, Classified by Skull Base site and Benign versus Malignant

Site	Benign	Malignant
Pituitary	56	0
Temporal bone	35	7
Infratemporal fossa	6	16
Anterior fossa	8	30
Middle fossa	6	16
Posterior fossa	4	0

DISCUSSION

The development of skull base surgery has presented a new, significantly challenging area for surgical pathologists. A review of our 7-year experience at the UCDMC for Skull Base Surgery confirms the profound diversity of lesions that occur in this complex anatomic

Table 2. Skull Base Surgery Cases by Pathologic Diagnosis and Site, 1990–1995, Center for Skull Base Surgery, University of California Davis

<i>Diagnosis</i>	<i>Site</i>	<i>Number</i>
Pituitary adenoma	Pituitary	55
Pituitary cyst	Pituitary	1
Schwannoma	Acoustic nerve/temporal	27
Schwannoma	Middle fossa	2
Schwannoma	Infratemporal fossa	1
Inverting papilloma	Anterior	3
Angiofibroma	Anterior	1
Hemangiopericytoma	Anterior	1
Chordoma	Clivus	2
Paraganglioma	Temporal	3
Meningioma	Middle fossa	4
Meningioma	Anterior fossa	4
Meningioma	Infratemporal fossa	2
Meningioma	Temporal	2
Meningioma	Posterior	2
Arthritic pannus	Posterior	2
Mucocele	Anterior	2
Epidermoid cyst	Temporal	2
Inflammatory pseudotumor	Infratemporal fossa	2
Fibrous dysplasia	Anterior	1
Squamous cell carcinoma	Middle fossa	10
Squamous cell carcinoma	Infratemporal fossa	10
Squamous cell carcinoma	Temporal	4
Squamous cell carcinoma	Anterior	8
Adenoid cystic carcinoma	Middle fossa	2
Adenoid cystic carcinoma	Anterior fossa	2
Melanoma	Anterior fossa	3
Olfactory neuroblastoma	Anterior	4
Olfactory neuroblastoma	Infratemporal fossa	1
Basal cell carcinoma	Anterior	2
Basal cell carcinoma	Infratemporal fossa	1
Basal cell carcinoma	Temporal	2
Nasopharyngeal carcinoma	Anterior	1
Lymphoma	Anterior	2
Malignant nerve sheath	Middle fossa	3
Malignant fibrous histiocytoma	Anterior	1
Alveolar rhabdomyosarcoma	Infratemporal	1
Leiomyosarcoma	Infratemporal	1
Sinonasal undifferentiated carcinoma	Anterior	4
Chondrosarcoma	Anterior	1
Dermatofibrosarcoma protuberans	Anterior	1
Metastatic renal cell carcinoma	Temporal	1
Metastatic prostate adenocarcinoma	Anterior	1
Mucoepidermoid carcinoma	Infratemporal	1
Carcinoma ex pleomorphic adenoma	Infratemporal	1

site. These lesions often have overlapping histologies that require meticulous detail to morphologic features and the consideration of a broad differential diagnosis. Our service has cared for a significant number, ie, 68, of patients with malignant lesions constituting 37% of our total clinical experience.

The challenge of differential diagnosis has been most acute in the areas of small round cell tumors and in undifferentiated malignancies. The scope of skull base lesions consisting of small, round cells include but are not limited to pituitary adenoma, lymphoma, olfactory neuroblastoma, neuroendocrine carcinoma, alveolar rhabdomyosarcoma, and inflammatory lesion. We en-

countered 10 small round cell lesions that required ancillary diagnostic studies. These included two invasive pituitary adenomas, two lymphomas, three olfactory neuroblastomas, one alveolar rhabdomyosarcoma, and two inflammatory lesions.

Both of the invasive pituitary adenomas presented as masses in the sphenoid sinuses with no endocrine manifestations. Initial biopsy interpretation on frozen section was “small round cell tumor.” The tissue sections were analyzed by IHC, including a panel of antibodies including markers for cells of lymphoid, neuroendocrine, rhabdoid, epithelial, and neural differentiation. The adenomas were marked with chromogranin A

(neurosecretory granules) and subsequently phenotyped with pituitary hormone-specific antibodies. Electron microscopy confirmed the presence of dense core neurosecretory granules.

Undifferentiated malignancies occur with some frequency in the sinonasal tract² and may present as skull base lesions. These typically aggressive tumors include malignant melanoma, sinonasal undifferentiated carcinoma, a variety of high-grade sarcomas, and high-grade olfactory neuroblastoma. The morphology is that of diffuse infiltrative sheets of pleomorphic ovoid and/or spindled cells with markedly variable nuclei. Many of these lesions have a high mitotic rate and necrosis. Sinonasal undifferentiated carcinoma (SNUC) is a rather recently described lesion that has histological and clinical features distinctive from olfactory neuroblastoma.³ Our four patients with SNUC presented with tumors extending into the anterior fossa. The differential diagnosis was perhaps most challenging in a 45-year-old woman who had a history of ductal carcinoma of breast with axillary metastases 3 years prior to presenting with an ethmoid sinus lesion. The tumor morphology was that of poorly differentiated ovoid cells in nests and sheets with focal necrosis, a high mitotic rate, and focal areas that suggested poorly formed glands. This pattern was in contrast to a review of sections from her mastectomy specimen, which was that of a moderately differentiated ductal carcinoma. Our workup included a panel of antibodies for IHC, analysis of estrogen and progesterone receptors, and electron microscopy. The tumor cells were reactive for low molecular weight cytokeratin and nonreactive to vimentin or neuroendocrine markers. Hormonal receptors were negative, and the ultrastructure showed poorly differentiated epithelial cells with no neurosecretory granules. Our final diagnosis, therefore, was SNUC.

We have previously discussed our frozen section experience in skull base surgery in 1993.⁴ An analysis of 39 surgeries performed between January 1990 and June 1992 showed an error rate of 3%, with two clinically significant discrepancies due to interpretive errors. We have carefully monitored our performance through

the continuous quality improvement program of the UCDCMC. Frozen section discrepancy rates from 1992 to 1996 ranged from 1.0 to 2.0% with a composite rate of 1.8%. All of these discrepancies have been due to sampling errors involving a "false-negative" frozen section diagnosis with discovery of tumor on the deeper permanent sections. In two patients, those sites represented a final surgical margin; however, to date no recurrence has been detected. Fifteen patients demonstrated insidious perineural spread that was unsuspected by imaging and clinical observation. This phenomenon was seen in all four of the adenoid cystic carcinoma cases, nine patients with squamous cell carcinoma, and two patients with sclerosing basal cell carcinoma.

These surgeries generated numerous frozen sections to ensure complete tumor resection. The most challenging of these was an adenoid cystic carcinoma of the ethmoid sinus and anterior, middle, and posterior fossa, which required 48 frozen sections.

Our 7-year experience with skull base surgery confirms the valuable role of the surgical pathologist as a member of the skull base team. The diversity of lesions that present at the skull base and the small and precious nature of the tissue samples require meticulous attention to both clinical and anatomic as well as morphologic considerations. The surgical pathologist and skull base surgeon must maintain vigilant communication to ensure the highest quality care for these challenging patients.

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