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REVIEW ARTICLE

Juvenile Nasopharyngeal Angiofibroma

WM Mendenhall,[1] JW Werning,[2] RW Hinerman,[1] RJ Amdur,[1] DB Villaret[2]

[1]Department of Radiation Oncology and [2]Department of Otolaryngology, University of Florida College of Medicine, Gainesville, Florida

ABSTRACT

Review of the literature was performed to define the optimal treatment of patients with juvenile nasopharyngeal angiofibroma. Patients with extracranial juvenile nasopharyngeal angiofibroma have a high likelihood of cure with acceptable morbidity after surgery alone. Transnasal endoscopic resection is highly successful for selected patients. Patients with intracranial extension, as well as patients with juvenile nasopharyngeal angiofibroma that recurs after prior resection, may be treated with either surgery or radiotherapy depending on the likelihood of achieving a complete resection with acceptable morbidity. The chance of cure after moderate dose radiotherapy is approximately 85%.

Key Words: *Angiofibroma, Pharyngeal neoplasms, Radiotherapy, Vascular neoplasms*

INTRODUCTION

Juvenile nasopharyngeal angiofibroma (JNA) is a benign, highly vascular tumour that often arises at the superior margin of the sphenopalatine foramen in adolescent males.[1-4] JNA is uncommon and accounts for approximately 0.5% of all head and neck neoplasms.[3] The median age at diagnosis is 15 years.[4,5] Presenting symptoms commonly include nasal obstruction and epistaxis.[4-6] Approximately 20% of patients have evidence of skull base invasion at the time of diagnosis.[3] JNAs may be hormonally dependent. Hagen et al studied androgen receptor binding in cultured tumour fibroblasts from 3 patients with JNA and demonstrated that cell proliferation increased with testosterone and decreased with antiandrogens.[7] Spontaneous regression is unlikely but has been observed.[8]

JNAs may be successfully treated with either surgery or radiotherapy (RT). There are limited data suggesting that chemotherapy may be efficacious for the occasional patient with an incompletely resected tumour that has recurred after RT.[9] The following is a discussion of the treatment of patients with JNA and, in particular, the role of RT.

Correspondence: *Dr William M Mendenhall, Department of Radiation Oncology, University of Florida Health Science Center, PO Box 100385, Gainesville, FL 32610-0385, USA.*
Tel: (1 352) 265 0287; Fax: (1 352) 265 0759;
E-mail: mendewil@shands.ufl.edu

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ENDPOINTS

The likelihood of death due to JNA is very low. Therefore, the efficacy of a particular treatment is evaluated based on local control and complications.

Local control after surgery implies complete removal of the JNA and no evidence of recurrence at follow-up physical examinations and/or radiographic studies. A more liberal definition of local control would include subtotal excision alone with no evidence of progression of untreated residual tumour. We would define this as locally persistent disease and thus a 'local failure'.

Local control after RT implies regression or stable disease without evidence of tumour progression. Benign tumours rarely regress completely after successful RT and may remain stable for many years. As long as there is no evidence of tumour progression, the tumour is as 'locally controlled' as if it had been completely resected without evidence of recurrence.[10-12]

Complications are coded as severe if they necessitate admission to hospital, surgical intervention, or result in death.[13]

STAGING

The purpose of a staging system is to stratify tumour extent so that the outcome may be predicted. Tumour extent is important to the surgeon for ascertaining the

Table 1. Staging systems for juvenile nasopharyngeal angiofibroma.[14-16]

Chandler et al,[14] 1984	Sessions et al,[15] 1981	Radkowski et al,[16] 1996
I Tumour confined to nasopharyngeal vault	IA Limited to nose and/or nasopharyngeal vault	IA Limited to nose and/or nasopharyngeal vault
II Tumour extending into nasal cavity or sphenoid sinus	IB Extension into ≥1 sinus	IB Extension into ≥1 sinus
III Tumour extending into antrum, ethmoid sinus, PMF, orbit, and/or cheek	IIA Minimal extension into PMF	IIA Minimal extension into PMF
IV Intracranial tumour	IIB Full occupation of PMF with or without erosion of orbital bones	IIB Full occupation of PMF with or without erosion of orbital bones
	IIC Infratemporal fossa with or without cheek invasion	IIC Or posterior to pterygoid plates
	III Intracranial extension	IIIA Erosion of skull base — minimal intracranial extension
		IIIB Erosion of skull base — extensive intracranial extension with or without cavernous sinus invasion

Abbreviation: PMF = pterygomaxillary fossa.

likelihood of complete excision and the risk of complications. Tumour extent is not related to the probability of local control after RT. However, the larger the tumour the more normal tissue must be included in the irradiated volume, so the risk of late effects may be higher for more extensive JNAs.

Optimal radiographic evaluation prior to treatment includes computed tomography (CT) and/or magnetic resonance imaging (MRI). Most patients will be treated surgically and undergo angiography with embolisation of the tumour prior to resection.

There is no universally accepted staging system for JNAs. Three commonly employed staging systems are depicted in Table 1.[14-16]

LOCAL CONTROL

Surgery

The results of surgery from 8 recently published series are shown in Table 2.[2,4,16-21] The proportion of patients with previously untreated tumours, as well as those with intracranial extension, varies with referral patterns. Patients in the University of Pittsburgh, USA, series were treated with endoscopic or endoscopic-assisted techniques.[20] Approximately 90% of patients underwent a complete resection; local control rates after surgery varied from 61% to 87%. Twenty percent of patients treated at the Hôpital Lariboisière in Paris had radiographically defined asymptomatic residual disease and were coded as being locally controlled for the purpose of their analysis.[2] Ultimate local control rates, including successful salvage for patients after local recurrence, ranged from 89% to 100%.

The likelihood of local control after surgery varies with tumour extent and the operation that is performed. Local control versus tumour stage for 44 patients treated at the Hôpital Lariboisière between 1985 and 1996 is depicted in Table 3.[2] An additional 11 patients were treated during the same period but were excluded from the analysis because of inadequate follow-up. The

Table 2. Recent results of surgery.[2,4,16-21]

Institution	Number of patients	Previously untreated (%)	Intracranial (%)	Follow-up (years)	Complete resection (%)	Local control after surgery (%)	Ultimate local control (%)
Mayo Clinic[4]	30	43	27	0.9-12.0	93	83	93
Zurich University Hospital[17]	15	53	80	Not stated	87	87	100
Toronto General Hospital[18]	14	—	7	1.0-9.5	—	64	93
Boston Children's Hospital[16]	23	96	22	Minimum, 1.0 Mean, 6.0	91	78	100
University of California (San Francisco)[19]	18	—	39	Not stated	89	61	89
University of Pittsburgh[20]	13	85	30	0.7-7.0 Median, 2.8	100	85	100
Hôpital Lariboisière[2]	44	80	66*	1.0-12.0 Median, 3.0	—	75†	—
University of Innsbruck[21]	14	—	7	1.0-13.0 Median, 5.5	—	86	—

* Radkowski stage IIIA (48%) and IIIB (18%).[16]

† Local recurrence defined as symptomatic residual disease.

Table 3. Results of surgery for 44 patients at the Hôpital Lariboisière in Paris.[2]

Stage*	Number of patients	Disease-free	Symptom-free†	Recurrence
IA	3	3	0	0
IB	4	3	1	0
IIC	8	5	2	1
IIIA	21	12	3	6
IIIB	8	1	3	4
Total	44	24 (55%)	9 (20%)	11 (25%)

*Staging from Radowski et al.[16]
†Asymptomatic radiographically defined residual tumour.

44 patients included in the study had follow-up from 1.0 to 12.0 years (median, 3.0 years; mean, 4.3 years). The likelihood of local control after surgery was inversely related to tumour extent.

Howard et al reported 39 previously untreated patients who were operated on at the Institute of Laryngology and Otology in London.[22] Patients underwent complete resection — the basisphenoid was routinely drilled out after 1 March 1998. Mean follow-up was 87 month (range, 3 to 11 years) for 20 patients treated before 1 March 1998, compared with 24 months (range, 7 to 36 months) for 19 patients treated after that date. Local control rates after surgery were as follows: before 1 March 1998, 12 of 20 patients (60%); after 1 March 1998, 19 of 19 patients (100%); and overall, 31 of 39 patients (79%).

Roger et al reported 20 patients who underwent exclusive endoscopic resection at 6 academic referral hospitals in France between 1995 and 2000.[5] Stage distribution according to the staging system of Radkowski et al was as follows:[16] stage IA, 2 patients; stage IB, 2 patients; stage IIA, 5 patients; stage IIB, 1 patient; stage IIC, 1 patient; and stage IIIA, 9 patients. Mean and median follow-up intervals were 22 and 15 months, respectively. Eighteen of 20 patients (90%) had a complete resection; the remaining 2 patients had small asymptomatic remnants of tumour after surgery.

Bales et al reported 5 patients with skull base invasion alone or in combination with intracranial extension who underwent a cranial facial resection at the University of Pennsylvania in Philadelphia and had follow-up from 28 to 63 months.[3] An unresectable local recurrence developed in 1 patient 19 months after surgery and was treated with RT. The remaining 4 patients remained disease-free. Close et al reported 6 patients with JNA involving the cavernous sinus who were treated surgically at the University of Texas Southwestern in Dallas between 1983 and 1988.[23] Five patients remained disease-free from 12 to 71 months after surgery. A local recurrence developed in 1 patient 10 months after surgery, and a second operation was performed.

Radiotherapy

The results of RT in 6 recent series are shown in Table 4.[6,24-28] Most patients included in these series had lesions that were recurrent after prior surgery and/or exhibited intracranial extension, and were thought to have a high likelihood of significant postoperative complications or incomplete resection. Thus, most patients were treated with RT by default. The local control rates after RT ranged from 73% to 100%. Tumour regression after successful RT is often slow. Cummings et al reported the largest series of patients irradiated for JNA and observed clinical evidence of residual tumour in 50% of patients 1 year after RT, and in 10% of patients 3 years after RT.[24] The median time to recurrence was 16 months (range, 12 to 101 months). Almost all patients who experience a local recurrence after RT undergo successful salvage therapy with an operation or a second course of RT, so that the probability of ultimate local control approaches 100% (Table 4).[6,24-28]

Table 4. Recent results of radiotherapy.[6,24-28]

Institution	Number of patients	Previously untreated (%)	Follow-up (years)	Dose/ fractionation	Local control after radiotherapy (%)	Ultimate local control (%)
Princess Margaret Hospital, Canada[24]	55	76	3.0-26.0	30-35 Gy/3 weeks	80	100
University of California (Los Angeles)[6]	27	—	Mean, 6.0*	30-55 Gy/3-6 weeks (36-39.6 Gy once daily since 1986)	85	100
University of Florida[25]	15	40	2.5-24.0 Median, 13.0	30-35 Gy/17-23 Fx	85	100
Washington University[26]	13	18	3.3-21.2 Median, 11.3	36-52 Gy 1.8-2 Gy/Fx	85	100
Cookridge Hospital, UK[27]	10	—	0.67-11.8 Median, 3.8	30-40 Gy 2 Gy/Fx	100	100
Baylor Medical School, USA[28]	15	67	1.0-14.0	32-46 Gy 2 Gy/Fx	73	100

Abbreviation: Fx = fractions. *1 patient lost to follow-up.

COMPLICATIONS

Surgery

Postoperative complications encountered in 44 patients treated surgically at the Hôpital Lariboisière between 1985 and 1996 included haemorrhage (2 patients), meningitis (1 patient), and amaurosis (1 patient).[2] Late complications included V2 dysesthesia (5 patients), lacrimal duct stenosis (4 patients), otitis media necessitating pressure equalisation tube placement (2 patients), and diplopia necessitating reconstruction of the orbital floor (2 patients).

Postoperative complications observed in 18 patients treated surgically at the University of California in San Francisco between 1980 and 1991 included cerebrospinal fluid leaks (2 patients), haemorrhage necessitating transfusion (1 patient), and transient oculomotor nerve palsy (1 patient).[19] Bremer et al reported the following complications in 30 patients who underwent surgery at the Mayo Clinic in the USA between 1972 and 1983: nasolacrimal duct stenosis (4 patients), haemorrhage (3 patients), exotropia (1 patient), mild proptosis (1 patient), and cheek numbness (1 patient).[4]

Roger et al reported 20 patients who underwent endoscopic resection between 1995 and 2000 and observed a mean blood loss of 350 cc (range, 50 cc to 750 cc).[5] No patients required a blood transfusion. Postoperative complications were limited to 2 patients who had infraorbital nerve paresis.

Close et al reported 6 patients who underwent resection of JNAs that involved the cavernous sinus and observed mild paresis of V2 and V3 in 3 patients.[23] Bales et al reported 5 patients who underwent a craniofacial resection at the University of Pennsylvania and observed a mean blood loss of 1120 cc (range, 700 cc to 1750 cc).[3] Two patients required a blood transfusion, 1 patient had anaesthesia of V2, and 1 patient had anaesthesia of V2 and V3.

Radiotherapy

Cummings et al reported 55 patients treated with RT and follow-up from 3 to 26 years.[24] Five complications were observed in 4 patients and included thyroid carcinoma (1 patient), basal cell carcinoma of the skin (1 patient), cataract (2 patients), and hypopituitarism (1 patient). Lee et al observed 5 late complications in 4 of 27 patients (15%) treated at the University of California in Los Angeles.[6] One patient developed panhypopituitarism, 3 patients developed cataracts, 1 patient exhibited growth abnormalities, and 1 patient developed temporal lobe necrosis and endophthalmitis. The latter patient received 30 Gy followed by a salvage craniofacial resection followed by an additional 45 Gy. Temporal lobectomy and enucleation of the ipsilateral eye were eventually required.

Five of 15 patients (33%) treated at the University of Florida developed complications, including delayed transient central nervous system (CNS) syndrome (1 patient), cataracts (3 patients), and basal cell carcinoma of the skin (1 patient). However, skin cancers are commonly encountered in Florida so that the latter 'complication' may be unrelated to RT.

CONCLUSIONS AND TREATMENT GUIDELINES

The likelihood of cure after surgery or RT is approximately 80% to 85%; the probability of ultimate local control approaches 100%. The vast majority of patients have lesions that are completely resectable with relatively limited morbidity and should be treated surgically. A small subset of patients present with recurrent and/or extensive tumours with significant intracranial invasion where the likelihood of complete resection with acceptable morbidity is modest. These patients are best treated with moderate-dose RT. The current dose fractionation schedule employed at the University of Florida is 35 Gy in 19 fractions administered once daily in a continuous course. There is no evidence that higher doses result in improved local control. Patients are optimally treated with megavoltage equipment using 3-dimensional CT-based treatment planning to ensure adequate coverage of the tumour while minimising the amount of normal tissues included in the fields. Use of current treatment planning technology will reduce the risk of a geographic miss and may improve the probability of local control. Most lesions are well covered with parallel opposed lateral fields. Tumours that exhibit significant anterior extension may be better treated using a heavily weighted anterior field and 1 or 2 lateral fields. The likelihood of significant complications with this approach is low.

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