Published in final edited form as:

Pediatr Blood Cancer. 2013 March ; 60(3): 371–376. doi:10.1002/pbc.24289.

Outcome Of Patients With Localized Orbital Sarcoma Who Relapsed Following Treatment On Intergroup Rhabdomyo-Sarcoma Study Group (IRSG) Protocols – III AND –IV, 1984-1997: A Report From The Children's Oncology Group

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Abstract

Background—We wanted to ascertain patterns of recurrence, re-treatment, and outcome among 188 eligible patients treated for localized orbital sarcoma on IRSG Protocols III/IV, 1984-1997.

Procedure—Retrospective chart review.

Results—Twenty-four of 188 patients (12.8%) developed local (n=22) or distant relapse (n=2) at 0.057-7.05 years (median, 1.58) after enrollment. Ages at study entry were 0.14-17 years (median, 5 years). Initial tumor operations included biopsy (n=20) or gross resection with microscopic residual (n=4). Initial tumor diameters were 0.5-7 cm (median, 3). Pathologic subtypes were embryonal rhabdomyosarcoma (ERMS, n=19), sarcoma not otherwise specified (n=2), and alveolar RMS, botryoid ERMS, or undifferentiated sarcoma (n=1 each). Initial treatment included vincristine/dactinomycin (n=24) including an alkylator (n=4) and radiotherapy (RT, n=21). Twenty patients responded, 14 completely, 6 partially. After recurrence, patients underwent orbital exenteration (n=10), enucleation (2), tumor excision (3), or biopsy (1); 7 had no operation, and 1 had no data. Post-relapse chemotherapy included combinations of etoposide (n=14 patients), doxorubicin (14), ifosfamide (12), cyclophosphamide (7), and dacarbazine (n=1). Six patients

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Presented in part by R. Beverly Raney, MD at the 42nd Annual Meeting of the International Society of Pediatric Oncology in Boston, MA on October 23, 2010.

received RT, including 4 previously treated and 2 not irradiated initially. Two patients died; one at 1.79 years after contralateral brain metastasis followed by local recurrence, and another at 2.49 years after multiple local recurrences. Twenty-two patients (91.7%) survived sarcoma-free for 0.04-17 years (median, 6.9) after relapse, and 18 of 22 (82%) were alive 5 years after relapse.

Conclusion—Survival following recurrent localized orbital sarcoma appears likely after vigorous re-treatment given with curative intent.

Keywords

Pediatric/Adolescent Orbital Sarcoma; Outcome After Recurrence

INTRODUCTION

The Intergroup Rhabdomyosarcoma Study Group (IRSG) was founded in 1972 to elucidate biology and improve therapy for young patients <21 years with newly diagnosed rhabdomyosarcoma (RMS) and undifferentiated soft-tissue sarcoma (UDS). Sequential protocols were designated IRS-I through IRS-IV.[1-4] Initial surgical treatment included either excision of localized tumor (complete with uninvolved margins, Group I; or grossly complete with microscopically involved margins with/without regional lymph-nodal spread, Group II), or biopsy only (Group III). These patients showed no clinical and/or radiographic evidence of distant metastases in lungs, bone marrow, bones, distant lymph nodes, or other organs, as detailed in relevant publications.[3,4] Patients then received chemotherapy with vincristine and dactinomycin (VA) (IRS-III, 1984-1991) or VA plus cyclophosphamide ± ifosfamide ± etoposide (IRS-IV, 1991-1997) for 1 to 2 years, depending on the protocol extant at the time. Radiation therapy (RT) was to be given to patients with residual microscopic or gross disease based on clinical and pathologic findings after initial surgical assessment. Treatment details can be found in the reports [3,4] and are outlined below under Patients and Methods.

The outcome for patients with localized RMS depends on the extent of disease at diagnosis, the amount of residual disease after initial surgical assessment and excision or biopsy, the primary site and size of the tumor, age of the patient, and histologic variety of RMS (embryonal, ERMS; or alveolar; ARMS). Both the IRSG experience and that of other soft-tissue sarcoma groups [3-7] have consistently found that patients with localized orbital RMS/UDS have an excellent prognosis for long-term disease-free survival and that the likelihood of distant metastases detectable at diagnosis is very low. The most predominant histologic subtype is ERMS, which has a favorable prognosis relative to ARMS and UDS. [8] In addition, most of the patients have small tumors that are readily apparent and could lead to early detection.

The purposes of this article are (1) to review the IRS-III/IV experience (1984-1997) with patients with localized orbital RMS/UDS, (2) to ascertain frequency and patterns of recurrence and re-treatment strategies, and (3) to assess outlook for long-term disease-free survival.

PATIENTS AND METHODS

One hundred eighty-eight eligible patients with localized orbital/eyelid rhabdomyosarcoma or undifferentiated sarcoma were enrolled on IRSG Protocols III (n=106) and IV (n=82) from 1984 to 1997. Members of the IRSG Surgical Subcommittee confirmed the type of operation done for obtaining diagnostic tissue, and members of the Pathology Subcommittee confirmed the diagnosis of ERMS, ARMS, UDS, or soft-tissue sarcoma not otherwise specified (Sarc NOS). Investigations looking for evidence of disease spread beyond the primary site included clinical and radiologic examinations, plus slides and sections of bone marrow samples and cerebrospinal fluid, as reported.[3,4]

Initial Treatment

Chemotherapy—Following signed informed consent by patient, parent, or guardian, chemotherapy with vincristine and dactinomycin (VA) was begun according to the Grouping system used to indicate the presence of residual disease (Group II, microscopic tumor at the margins; or Group III, gross residual disease ± tumor-involved regional lymph nodes). No tumors were completely removed with microscopically uninvolved tumor margins (Group I). IRS-III patients with localized orbital tumors received vincristine and dactinomycin for 54 weeks without an alkylating agent (see Figure 1 on page 613, Reference 3). IRS-IV patients in Group II received VA as in IRS-III, but for 32 rather than 54 weeks.[4] IRS-IV Group III patients were part of a three-way randomized trial of VA + cyclophosphamide (VAC) versus VA + ifosfamide (VAI) versus VI + etoposide (VIE) for 28 weeks, followed by VAC finishing at week 43 (see Figure 1 on page 3093 of Reference 4). *Radiation Therapy (RT)*. IRS-III Group II patients received a total of 41.4 Gray (Gy) delivered conventionally (once daily, 5 days per week), or if in Group III and < 6 years old with tumors < 5 cm, beginning on week 2. The total RT dose was higher, 45 to 50.4 Gy, for Group III patients who were 6 years or older with small tumors or with tumors 5 cm or larger, beginning on week 6.[9] IRS-IV Group II patients received 41.4 Gy as in IRS-III. Group III patients were randomized to receive conventional RT to a total dose of 50.4 Gy *versus* 59.4 Gy delivered twice daily (hyperfractionated RT), beginning on week 9.[10] As there were no statistical differences between the outcomes of IRS-IV randomizations for chemotherapy and RT [4,10], they are considered together in this report.

IRSG Pediatric Oncologists reviewed the treatments received by the patients for compliance with the protocol-recommended doses and schedules, and IRSG Radiation Therapists reviewed the patients treated with primary RT for protocol compliance. Patients were then followed periodically for tumor response, and late effects after end of therapy were assessed in some patients by tabulating results of questionnaires completed by the enrolling institution.[11] Charts of patients who developed recurrent disease were then reviewed to determine the initial pre-treatment parameters of interest (patient age, gender; tumor size [widest diameter in cm], histology; extent of disease, Group), plus treatment, response, site(s) and time to relapse; further therapy, and overall survival. All patients with localized orbital tumor were categorized in Stage 1 because of their favorable prognosis.[4]

RESULTS

From 1984 to 1997, 188 eligible patients with localized orbital sarcoma were enrolled on IRS-III and IRS-IV. Subsequently, 24 patients (12.8%) developed recurrent disease. Relapse rates were 18 of 106 (17%) on IRS-III and 6 of 82 (7%) on IRS-IV.

Patients and Tumors

The characteristics of the patients and tumors and initial treatment of the 24 patients experiencing progressive or recurrent disease are shown in Table I. The patients' ages at study entry were 0.14 to 17 years (median, 5 years); 17 were males and 7 were females (M:F, 2.4:1). Nineteen of the tumors arose in the orbit, 4 in an eyelid and 1 in a lateral rectus muscle. One patient's tumor involved orbital bone by limited contiguous erosion. Twenty patients had localized, gross residual disease (Group III), and 4 had microscopic residual disease after grossly complete excision, 3 in an eyelid and 1 in the orbit, without evident regional lymph-nodal spread (Group IIA, 2 on IRS-III and 2 on IRS-IV). Regional lymph node involvement at diagnosis was absent (N0) in 20 patients and unknown (NX) in 4. Tumors' initial size (widest diameter) ranged from 0.5 to 7 cm (median, 3). Histologic subtypes were 19 ERMS, 2 sarcoma NOS, and 1 each of botryoid ERMS, ARMS, and UDS.

Primary Treatment and Compliance with Protocol Guidelines

Chemotherapy (Table I)—All patients received vincristine and dactinomycin (VA). Initially, 1 of the 4 IRS-IV Group III patients received VA+cyclophosphamide and 3 received VA+ifosfamide. Four with Group IIA tumors, 2 in IRS-III and 2 in IRS-IV, received VA. **Radiation Therapy (Table II)**. Twenty-one patients (87.5%) received primary RT in doses ranging from 35.7 Gray (Gy) to 54.2 Gy (median, 41.4 Gy). Nineteen patients (86%) received doses appropriate for the patients' age and Group (IIA patients should receive 41.4 Gy, Group III patients should receive 45-54 Gy). Two patients received less than protocol-directed doses: patient 19, 6 years old, had a Group III eyelid tumor and received only 35.7 Gy; patient 22, 7 months old, was randomized to receive 59 Gy by hyperfractionation, but received only 50.6 Gy; the chart had no notation about why the dose was limited. Three patients received no primary RT: patient 9, seven weeks old, had increasing local tumor growth at week 3 and then received etoposide, ifosfamide, and RT; patient 17, 10 years old, had a Group IIA tumor and no reason stated for omitting primary RT; patient 23, 13 years old, had a sibling at home with cerebral palsy and the parents could not travel to the RT facility due to the sibling's disability.

Response to Primary Therapy (Table II)

The best responses to initial treatment were complete disappearance of tumor in 14 patients (58%) and partial shrinkage (50%-99%) in 6 (25%).^[3] Patients with less than a partial response included 1 with no response and 3 with locally increasing disease (17%).

Site(s) and Timing of First Recurrence

Recurrences were local in 22 patients (including 1 each with extension into the adjacent cavernous sinus or maxillary antrum) and distant in 2 (ipsilateral parotid gland, contralateral brain parenchyma). No patient was diagnosed with extension of tumor into the cerebrospinal

fluid. Times to recurrence ranged from 3 weeks (0.057 years) to 7 years (median, 1.58 years). The three patients whose tumors increased in size after treatment came off study at 0.057, 0.21, and 0.61 years, respectively. The first, a 10-week-old infant, had received no RT; the other two had received 45 Gy, both within protocol guidelines. Three patients had “late” local recurrences at 5.8, 6.48, and 7 years, respectively. The first had received a low dose of RT, but the other two had received RT within protocol guidelines.

Subsequent Treatment

There was no protocol-suggested outline of procedures and treatments to consider following relapse, so each group of physicians decided on a plan according to their best judgment about each patient. Table II shows the types of salvage therapy for 23 patients after recurrence, in order of the interventions made (patient number 21 had no data about subsequent management).

Chemotherapy—Thirteen patients received chemotherapy initially; 8 of them went on to have a surgical procedure (n=3), to receive RT (2), or both (3). *Surgery*. Nine patients initially underwent a surgical procedure, and afterwards 5 of them received additional chemotherapy (n=3), RT, or both (n=1 each). Altogether 10 patients underwent orbital exenteration; 2 had enucleation of the globe, 3 underwent tumor excision, and 1 had only a biopsy. Only 4 patients were treated with all three modalities of surgery, RT, and chemotherapy following first relapse, but data were limited regarding additional modalities in 5 other patients.

Survival After Recurrence (Table II)

Twenty-two of the 24 patients (91.7%) were alive and free of recurrent tumor at a median of 6.9 years after relapse (range, 0.04 to 17 years). Eighteen of the 22 patients (82%) were in continuous remission for 5 years or more. The other 4 were followed for 0.04, 0.68, 0.85, and 3.3 years, respectively, so no statement can be made about their likelihood of 5-year survival after relapse. All of the 3 patients who relapsed early with increasing local tumor growth and the 3 with late relapses were alive at last followup.

Two patients died, both with ERMS

One succumbed with recurrent local tumor at 1.8 years after an earlier isolated distant recurrence in contralateral brain parenchyma, and the other died with recurrent local tumor at 2.5 years following initial relapse.

Second Malignant Neoplasm

Six years after local recurrence of embryonal RMS, initially treated with VA and 45 Gray of RT within protocol guidelines, patient 12 was diagnosed with a mucoepithelial carcinoma of the ipsilateral parotid gland. The patient was alive nearly 5 years after the carcinoma was treated.

Prognostic Factors

An analysis of prognostic factors for event-free survival of patients with localized orbital RMS treated on IRS-III/IV revealed none predictive of outcome. However, most children with localized orbital primaries were 1-9 years old and had Group III, noninvasive, small embryonal tumors, all considered favorable. There was no difference in outcome by gender.

DISCUSSION

Because most patients with primary orbital RMS present with small, localized, favorable-histology (embryonal) tumors, and thus have a good outlook for survival, many investigators limit the initial surgical procedure to a biopsy only (Group III), unless the mass is easily accessible in an eyelid and can be grossly removed (Group II). The latter procedure is worthwhile when feasible, because current Children's Oncology Group (COG) protocols recommend a lower dose of RT for patients with no visible residual disease prior to initial chemotherapy compared to those with gross residual tumor. The excellent survival results reflect a divergence in philosophy regarding the necessity for RT in patients with localized, gross residual tumor when chemotherapy is begun after diagnosis. The IRSG and subsequent COG philosophy is that RT should be given to patients with residual orbital/eyelid disease, both microscopic and gross, to provide patients the greatest likelihood of having durable local control and remaining relapse-free.

Short-term effects of orbital RT include increased lacrimation and inflammation of the area treated, which are more problematic in young children and those treated with higher doses. Long-term effects include induction of cataracts; irritated, painful, and/or dry eye; lacrimal duct stenosis; failure of growth of orbital bone, and statural growth failure due to suppression of pituitary growth hormone by RT.[11-13]

Because of these concerns, some European groups prefer the approach of initial diagnostic biopsy followed by chemotherapy, employing delayed primary surgical removal if complete response is not achieved and deferring RT until it becomes clear that RT is necessary to obtain local control and preserve the globe.[13] Thus, deleterious side-effects of RT on tissues of the eye and orbit can be avoided in approximately 40% of patients with orbital tumors.[13] Nevertheless, this approach entails the necessity of toxic salvage therapy for the approximately 44% of patients who have a local recurrence, some of whom fail to survive. In an important Editorial, Donaldson and Anderson presented the comparative data for all primary site categories in the European MMT-89 trial *versus* the IRS-IV trial: survival of orbital patients at 5 years was 85% in the MMT-89 trial and 100% in the IRS-IV trial.[14]

The excellent prognosis for patients with localized orbital RMS has been documented in successive studies from the IRSG and several European cooperative groups.[2-7,13] The outlook for orbital patients with favorable histology (ERMS) is better after recurrence than it is for those with unfavorable histology (ARMS or UDS).[8,15-18] Most recurrences are local and usually occur within four years after initial therapy. However, an occasional relapse occurs after 5 years [19], as in 3 of our patients (12.5%)

Because patients with localized orbital sarcoma usually have a good prognosis and thus a low rate of recurrence, there are only a few series which report treatment and outcome for patients with relapsed or refractory orbital sarcoma. The largest, reported in 2001 [11], was a collaborative effort involving the IRSG, the International Society of Pediatric Oncology (SIOP), the German Cooperative Soft Tissue Sarcoma (CWS) Group, and the Italian Cooperative Soft Tissue Sarcoma Group (ICG). Three hundred six patients who were enrolled with localized, N0 (uninvolved regional lymph nodes) orbital sarcoma between 1978 and 1992 were assessed for event-free survival (EFS) and overall survival, as well as for late effects of the disease and therapy. Only 37% (n=16) of the 43 SIOP patients received primary RT because they did not have a clinical complete remission after 4 courses of chemotherapy, whereas 70% to 93% of the other 263 patients received primary RT. EFS rates at 10 years were 86% for the IRSG patients, 70% for the CWS patients, 64% for the ICG patients, and 58% for the SIOP patients, $P<0.001$ for the difference between the IRSG and the European groups. Patients who received primary RT had a 10-year EFS rate of 82% compared to 53% for those who received no primary RT, $P<0.001$. However, the overall survival rates were nearly identical at 10 years, 87% for those irradiated initially and 86% of those who were not, suggesting that a significant number of patients could be cured after relapse by receiving RT afterward. Fifty-one of the 306 patients (17%) developed a recurrence. Only 2 relapses occurred more than 5 years after diagnosis. The types of relapse were local (n=47 patients, 3 of whom also had distant metastases) and distant only (n=4 patients). Among the 47 patients with local relapse, 27 of 61 occurred in non-irradiated patients (44%) versus 20 of 245 irradiated patients (8%). The rates of local relapse were 5% for the IRSG, 30% for the CWS, and 35 or 36 % for the ICG and SIOP, respectively.[11]

In a series of 30 consecutive patients with orbital sarcoma (27 with ERMS and 3 with ARMS), 6 patients (20%) developed local recurrence, 1 regional lymph node metastasis, and 1 distant metastases. One patient died with distant metastases. None of these patients was designated in the report as refractory to primary therapy.[20]

In another study of 10 patients with localized ERMS of the orbit, 5 had recurrent tumor after initial remission, and 5 had persistent tumor with local progression, considered as having refractory disease. All 10 had previously received multiagent chemotherapy, and 8 had also received external-beam RT. They then were treated with intensity-modulated brachytherapy (IMBT) with Iridium¹⁹² following tumor removal or debulking, with the intent of preserving the globe. Four children died of tumor; one was alive with disease, and 5 survived without evidence of recurrence for 1 to 10 years after IMBT.[21]

In another series of 67 patients with localized orbital ERMS, 7 patients (10.4%) had refractory local disease despite chemotherapy and RT, defined as those with orbital recurrence and those with incomplete disappearance of tumor after primary therapy. They were treated surgically with exenteration (n=5) or eye-sparing tumor excision plus further chemotherapy (n=2). Five of those children (71%) survived disease-free for 3.2 to 10 years. [22] Of note is that all of our four patients with increasing disease or no response (numbers 2, 3, 9, 23) were alive and disease-free for more than 5 years after initiation of salvage therapy.

Despite variable treatments for recurrent or refractory disease, we observed a high rate of overall survival, 91.7%, and 18 of the 22 survivors (82%) were continuously disease-free for 5 years or more after recurrence. This rate of 5-year post-recurrence survival is somewhat better than that of our previously reported experience with patients who relapsed after treatment for Stage 1 ERMS on IRSG Protocols -III, -IV Pilot, and -IV, reported in 1999. [23] That rate at 5 years was 72% after local recurrence. Thus we believe that cure can be possible for young patients with recurrence after initial treatment for localized orbital soft-tissue sarcoma, provided that local control can be achieved and that no regional or distant metastases appear as the retrieval therapy and observation period proceed. We cannot state which approach is best, but usually utilizing surgery (at the least, a biopsy to confirm the nature of the recurrence), chemotherapy, and RT (external-beam, or brachytherapy if feasible), may all have a role. Retrieval or salvage treatment must be individualized according to each patient's previous history and ability to tolerate further toxic agents and methods to achieve local control.

Acknowledgments

Supported in part by Grants CA-24507, CA-29511, CA-72989, and CA-98543 from the National Cancer Institute, Bethesda, Maryland, USA. A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 is available online at <http://www.childrensoncologygroup.org/admin/grantinfo.htm>

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TABLE I

Characteristics And Initial Treatment Of 24 IRSG Patients With Localized Orbital Rhabdomyosarcoma, Undifferentiated Sarcoma, Or Soft-tissue Sarcoma Not Otherwise Specified, Who Subsequently Developed Recurrent Sarcoma *

Patient Number	Age in Years, Gender	Site, Tumor Diameter (cm); T, N Stage	Disease Extension at Diagnosis	Group	Pathology	Treatment Regimen
1	1.7M	R Orbit, 4.5; T1, NX		III	Emb	VA+RT
2	8M	Orbit, 3; TX, NX		III	Emb	VA+RT
3	4M	Orbit, 4; T2, N0		III	Emb	VA+RT
4	5F	Orbit, 2; T1, N0		III	Emb	VA+RT
5	12M	Orbit, <5; T1, N0		III	Emb	VA+RT
6	6M	Orbit, 2; T1, N0		III	Emb	VA+RT
7	2M	Orbit, 3; T2, NX	Orbital bone erosion	III	Emb	VA+RT
8	7M	Orbit, 2; T1, N0		III	Emb	VA+RT
9	0.14F	Orbit, 1.5; T1, N0		III	Undif Sarc, Institut'nl	VA, no 1° RT
10	5M	Orbit, 0.5; T1, N0	No CSF exam at diagnosis	III	Emb	VA+RT
11	5M	Orbit, 3.5; T1, N0		III	Emb	VA+RT
12	6M	L Orbit, 2; T1, N0		III	Emb	VA+RT
13	5M	Orbit, 2.5; T1, N0	No CSF exam at diagnosis	IIA	Emb	VA+RT
14	17M	Orbit, 4; TX, N0		III	Sarc NOS	VA+RT
15	10M	Orbit, 3; T1, N0		III	Sarc NOS	VA+RT
16	5M	Rectus, 3; T1, N0		III	Emb	VA+RT
17	10F	Eyelid, 2.5; T1, N0		IIA	Emb	VA; no 1° RT
18	5M	Orbit, 3; T1, NX		III	Emb	VA+RT
19	6F	Eyelid, 4.5; T1, N0		III	Emb	VAI+RT
20	10.9F	Orbit, 2.5; T1, N0	No CSF exam at diagnosis	III	Emb	VAI+RT
21	5F	Eyelid, 1; T1, N0	No CSF exam at diagnosis	IIA	Emb	VA+RT
22	0.6F	R Orbit, 4.5; T1, N0		III	Alv	VAC+RT
23	13M	Orbit, 7; T2, N0	No CSF or BM exam at diagnosis	III	Emb	VAI; A to VAC at parental request; no 1° RT
24	5M	Eyelid, <1/2; T1, N0	No CSF exam at diagnosis; tumor re-excised 1 week later	IIA	Bot Emb, Institut'nl	VA+RT

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* Abbreviations: M, male; F, female; T1, tumor non-invasive of adjacent structures; T2, tumor invasive; TX, unknown invasiveness; N0, no regional lymph-node involvement; N1, tumor involved regional lymph nodes; NX, unknown regional lymph-node status; R, right; L, left; cm, centimeters; exam, examination; CSF, cerebrospinal fluid; BM, bone marrow; Emb, embryonal rhabdomyosarcoma (RMS); Alv, alveolar RMS; Undif Sarc, undifferentiated sarcoma; Institut'nl, institutional (no central pathology evaluation); Sarc NOS, sarcoma not otherwise specified; Bot, botryoid Emb RMS; V, vincristine; A, dactinomycin; C, cyclophosphamide; I, ifosfamide; RT, radiation therapy; 1^o, primary; , changed; parental request: patient's sibling had cerebral palsy.

TABLE II

Best Response Of 24 IRSG Patients With Localized Orbital Rhabdomyosarcoma, Undifferentiated Sarcoma, Or Soft-tissue Sarcoma Not Otherwise Specified, Who Later Relapsed: Salvage Treatment And Survival*

Patient Number	Best Response	RT (Gray) Prior to Relapse; Evaluation	Sites of Relapse	Time to Relapse in Years	Salvage Therapy	Years After 1° Relapse; + = Alive
1	CR	50.4; WPG	[1]: L parietal brain met., anaplastic ERMS [2]: local recurrence	2.62 0.38 after [1]	~90% tumor removal, no other data	Died due to tumor, 1.79
2	Inc.Dis.	45; WPG	Local	0.613	Exenteration; E, I	8.41 +
3	Inc.Dis.	45.0; WPG	Local	0.210	V, C, D	12.8+
4	PR	48.6; WPG	Local	1.11	C, D, E, P; gross total excision of tumor	8.12+
5	PR	50.4; WPG	Local	1.69	E, I x2; enucleation; D, DTIC x6, Exent.	6.87+
6	PR	45; WPG	Local	1.31	V,C,D,E,P; Exent.; RT	17.0+
7	PR	54.2; rate too slow	Local	0.985	C, D, E, P; Exent.; brachy. RT for microresidual tumor	11.1+
8	CR	45; WPG	Local, extended to cavernous sinus	2.30	Enucleation; D, E, I, P	0.043+
9	Inc.Dis.	0; MPD	Local; no chemo after day 22	0.057	E, I; RT	7.58+
10	CR	41.4; WPG	Local	7.05	Exent.; no other data	3.37+
11	CR	41.4; volume too large	Local	1.08	D, E, I, P	7.49+
12	CR	45; WPG	[1] Local [2] L parotid mucocellular carcinoma: SMN	[1] 1.5 [2] 6.0 after [1]	[1] D, I [2] No information	13.3+
13	CR	41.4; WPG	Local	1.57	Exent.; V, C, D	6.48+
14	CR	50.4; WPG	Local	0.785	E, I	0.679+
15	CR	50.4; WPG	Local, extended to maxillary antrum	6.43	E, I; followed by V, A, C	0.846+
16	PR	45; WPG	Local	1.59	Exent.; V, C, D, E, I	10.2+
17	CR	0; MPD	[1] Local [2] Local	1.69 3.89	Exent., V, C, D, I; RT 45 Gray Taxol	Died due to tumor, 2.49
18	PR	41.4; MPD, volume low	Local,	0.914	C, D, E, I; RT	13.0+
19	CR	35.7; dose low	Local	5.75	V, D, E; RT, 50 Gy; tumorectomy	8.13+

Patient Number	Best Response	RT (Gray) Prior to Relapse; Evaluation	Sites of Relapse	Time to Relapse in Years	Salvage Therapy	Years After 1 ^o Relapse; + = Alive
20	CR	50.4; WPG	Local	2.03	Enucleation; P; no other data	6.13+
21	CR	41.4; WPG	Local	1.84	Biopsy pos.; no other data	5.84+
22	CR	50.6; HF-RT dose too low	R Parotid, with 1 pos., 2 neg. node biopsies	2.39	No data	5.74+
23	NR	0, MPD; sibling with cerebral palsy at home	Local, multiple times; invaded frontal lobe	1.29	Exenteration, RT; later, cystic brain necrosis	6.71+
24	CR	41.4; WPG	Local	1.14	E, I; Exent.; D, V	5.03+

* Abbreviations: See Table 1; CR, complete response; PR, partial response; Inc. Dis., increasing disease (local progression); NR, no response; WPG, within protocol guidelines; MPD, major protocol deviation; D, doxorubicin; DTIC, dimethyl triazeno imidazole carboxamide (dacarbazine); E, etoposide; P, cisplatin; R, right; L, left; pos., positive (tumor present); neg., negative (tumor not present); Exent., orbital exenteration; SMN, second malignant neoplasm; brachy, RT, brachytherapy; AWD, alive with disease; met., metastasis; 1^o, first.