The Laryngoscope
Lippincott Williams & Wilkins, Inc., Philadelphia

Sinonasal Undifferentiated Carcinoma: The Search for a Better Outcome

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Objective: **To evaluate the clinical outcomes of a standardized treatment approach for sinonasal undifferentiated carcinoma (SNUC).** ***Study Design:*** **Single-center, retrospective case series.** ***Methods:*** **Fifteen patients with newly diagnosed SNUC were seen in the Department of Otolaryngology–Head and Neck Surgery at the University of Virginia from 1991 to 2000. Long-term follow-up on five additional patients diagnosed between 1986 and 1991 was also analyzed.** ***Results:*** **Overall, 10 patients were treated with curative intent with neoadjuvant chemoradiotherapy followed by craniofacial resection (CFR). The majority of the remainder was treated with palliative radiotherapy or chemoradiotherapy alone. Four patients who underwent CFR are currently free of disease at 4, 36, 49, and 164 months postoperatively. The 2-year survival of all evaluable patients, regardless of treatment, was 47%. Two-year survival was 64% in the group treated by CFR and 25% in the group treated with chemo- and/or radiotherapy ($P = .076$).** ***Conclusion:*** **For patients with good performance status and limited intracranial or intraorbital disease, we continue to advocate initial chemoradiotherapy followed by craniofacial resection. Patients who are deemed inoperable as a result of advanced disease may nevertheless experience significant palliation with chemoradiotherapy only.** ***Key Words:*** **Head and neck neoplasms, sinonasal undifferentiated carcinoma, craniofacial resection.**

Laryngoscope, **112:1450–1455, 2002**

INTRODUCTION

In 1986, Frierson et al.[1] provided the first description of the clinicopathologic characteristics of sinonasal undifferentiated carcinoma (SNUC), an aggressive neoplasm arising within the nasal cavity or paranasal sinuses. It is differentiated pathologically from other superior nasal vault neoplasms by its nuclear pleomorphism, high nuclear-to-cytoplasm ratios, numerous mitoses, vascular invasion, and absence of glandular differentiation. In some cases, the adjacent mucosa is severely dysplastic, suggesting that the tissue of origin may be the Schneiderian epithelium.

Like would be expected from its anaplastic appearance, SNUC behaves aggressively. In the original case series reported by Levine et al.,[2] advanced local disease at the time of diagnosis was the norm, with 6 and 7 of 11 patients presenting with orbital and cranial cavity involvement, respectively. Distant metastases at presentation were seen in 3 of 11 patients. Overall cause-specific survival for this series was 9%. In 1993, Levine and Deutsch reported an additional 6 patients with SNUC.[3] Of these, 3 had no evidence of intracranial or orbital disease at diagnosis and underwent sequential chemotherapy, radiotherapy, and surgical resection. At the time of the report, all 3 were alive with no evidence of disease at a mean of 53.6 months from the time of diagnosis. From this experience, a standardized approach for the treatment of patients with SNUC was adopted. This article reports the outcomes of treatment using this approach.

MATERIALS AND METHODS

Patients diagnosed with SNUC between January 1986 and October 1991, and between November 1991 and October 2000, were identified by review of records from the Department of Otolaryngology–Head and Neck Surgery, Department of Pathology, and McIntire Tumor Registry at the University of Virginia. All clinical information was determined by retrospective chart review. In the case of patients who were moribund and/or who had advanced, uncontrolled disease at the time of last follow-up, and for whom outcome could not be determined by chart review, date of death was determined from review of Social Security Administration statistics. The cause of death in such cases was assumed to have been SNUC rather than intercurrent disease. Univariate survival analysis for the group as a whole and stratified by treatment type was carried out using the Kaplan-Meier method.

RESULTS

Fifteen patients with SNUC were seen in the Department of Otolaryngology at the University of Virginia between November 1991 and October 2000. There were 14 men and 1 woman, with a mean age of 58 years. Mean duration of symptoms before diagnosis was 4.2 ± 3.8

Presented at the Head & Neck Society Section of the Triological Society Meeting, Palm Desert, CA, May 16, 2001.

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Editor's Note: This Manuscript was accepted for publication April 29, 2002.

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months. Eight patients (53%) presented with epistaxis or bloody rhinorrhea and 6 (47%) had visual acuity changes, diplopia, or other ocular symptoms. Nasal obstruction, headache, or facial pain were other frequent presenting symptoms. No significant epidemiologic associations could be identified, perhaps in part because of the small sample size. Extensive local disease at the time of diagnosis was common. Staging was according to the Kadish system[4] and was based on a combination of rigid nasal endoscopy, computed tomography, and magnetic resonance imaging. Ten patients (73%) were Kadish C and 4 (27%) were Kadish B. Eight patients (53%) had intracranial disease with dural involvement, but in no case did the tumor involve brain parenchyma. Periorbital and orbital involvement were seen in 6 (40%) and 5 (33%) patients, respectively. The cavernous sinus was invaded in 5 patients (33%). For a further breakdown of subsite involvement, see Figure 1. Two patients (13%) presented with regional metastasis and none were found to have distant metastases at the time of diagnosis, although 1 patient was found to have cervical vertebral metastases 1 month after diagnosis. Staging studies other than chest radiographs and liver function tests were not performed unless dictated by symptoms or abnormalities of these screening tests.

In all cases, treatment involved radiotherapy. When radiotherapy was used preoperatively, the dose was 5000 to 5400 cGy in 25 fractions. When used palliatively, either alone or in combination with chemotherapy, the dose ranged from 5500 to 6330 cGy. In two cases, the patients received radiotherapy at another facility and the ultimate dose could not be determined.

Eleven patients also received chemotherapy as part of their initial treatment. Of these, 8 received the standard cyclophosphamide/doxorubicin/vincristine (CAV) regimen before radiotherapy. By protocol, three cycles were given at 3-week intervals.[3] However, in certain cases this regimen was modified based an apparent lack of response of the tumor. Of the 8 patients who received CAV, 2 were switched to etoposide and cisplatin after no response was seen after one or two cycles of CAV. One of these patients (no. 13) is currently alive with no evidence of disease, although he has had two recurrences after a craniofacial resection, both treated surgically. The others completed two (2 patients), three (3 patients), or four (1 patient) cycles.

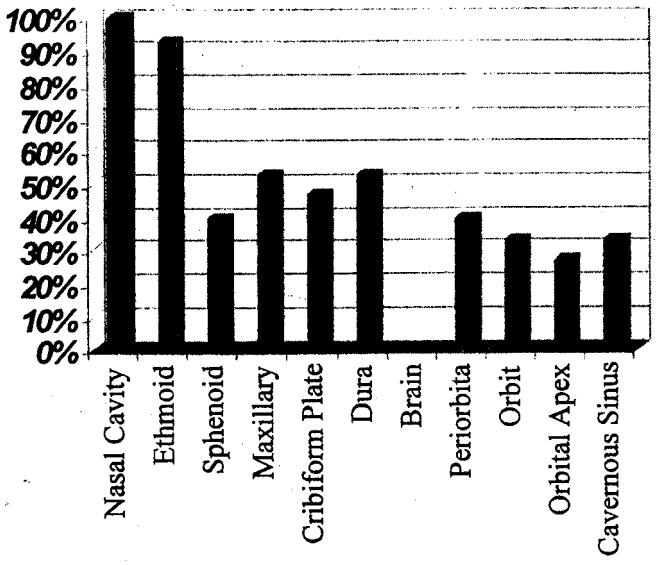

Fig. 1. Local extent of disease for patients with SNUC (1991–2000).

One patient received initial treatment with cisplatin and 5-fluorouracil at another institution before evaluation at the University of Virginia. After completion of concomitant chemoradiotherapy, he was re-evaluated and still felt to be unresectable based on residual disease in the cavernous sinus. Two patients, treated with chemotherapy at the University of Virginia, received an alternative etoposide/platinum-based regimen.

In the 4 patients who received no initial chemotherapy, 3 had poor performance status and extensive local disease, and were treated with palliative radiotherapy only. The last patient was initially diagnosed with squamous cell carcinoma (SCCA) and treated with preoperative radiotherapy followed by a radical maxillectomy at another institution. He recurred in the frontal and ethmoid sinuses 2 years later, at which time a biopsy evaluated at the University of Virginia was read as SNUC. He then underwent salvage CFR, but recurred a second time in the nasopharynx and at that time was palliated with additional radiotherapy, etoposide, cisplatin, and methotrexate.

Surgical resection was offered to 9 of 15 patients (60%) as part of the initial treatment plan. The decision to recommend surgery was based primarily on pretreatment staging. In one case (no. 10), a patient who had locally advanced disease at the time of diagnosis, including at the orbital apex, was noted to have a dramatic response to adjuvant chemotherapy. This patient was subsequently offered and accepted a CFR despite the fact that his tumor was initially considered unresectable. In accepting the surgery, he was fully cognizant of the fact that this represented a departure from the standard treatment algorithm and was willing to accept the attendant risks. An eye-sparing CFR was performed and this patient is free of disease at 49 months. Considering all patients who were treated surgically, 8 underwent CFR through a combined frontal craniotomy/lateral rhinotomy approach. The ninth patient (no. 8) was the one originally misdiagnosed as SCCA who underwent a radical maxillectomy. Of the 8 patients who underwent CFR primarily, one (no. 5) had the procedure aborted as a result of extensive orbital apex involvement found at the time of surgery. Margins were controlled by intraoperative frozen section analysis when necessary. In the case of extensive periorbital resection, reconstruction with a fascial autograft was performed. No patients required orbital exenteration to obtain negative margins. Closure of the resulting anterior cranial fossa defect is routinely performed in layers with a pericranial flap, abdominal fat/fascia, and split-thickness skin graft. Nasal packing is used to support the reconstruction and is left in place for 10 days. No patients required tracheotomy.

A group of 5 additional patients who were diagnosed between 1986 and 1991 and who had follow-up for a min-

imum of 5 years, or until their death, was also identified. These patients had been treated using the same principles as the later group, with sequential CAV chemotherapy, radiotherapy, and in 2 cases CFR. The combined group of 20 patients, comprising all individuals with sufficient follow-up treated for SNUC at the University of Virginia between 1986 and 2000 and shown in Table I, is the basis of the following analyses.

There was no perioperative mortality. Major complications were few. Two patients developed cerebrospinal fluid leaks. One of these was successfully treated with serial lumbar punctures, whereas the second was refractory to conservative treatment and eventually required operative repair. Two patients were noted to have temporary mental status changes attributed to pneumocephalus. Late complications included 1 patient with a sinocutaneous fistula. Another patient developed symptomatic nasal obstruction resulting from synechiae, which were successfully lysed in the clinic. This complication was also noted in 1 patient treated with chemoradiotherapy alone.

To determine the effectiveness of neoadjuvant therapy, the pathology reports from the 10 patients who underwent CFR as part of their initial treatment were examined. Three, all of whom had received CAV-based chemotherapy, had no evidence of residual tumor in the surgical specimen. Of the remaining 7, 2 had positive margins or gross residual disease (patient no. 5), 3 had close margins, and 2 had clear margins. Considering the 5 patients in whom complete extirpation of tumor was demonstrated, three were without evidence of disease at a mean of 36 months. A fourth, who had a complete local response to neoadjuvant 3, died of distant metastases at 19 months. The fifth patient (no. 20) died of unresectable local recurrence at 97 months. Of the remaining 5 who had either positive or close margins, only 1 patient (no. 18) who had a close margin was free of disease at 164 months, with the remaining 4 dead of disease at a mean of 13 months. Statistical analysis using Fisher's exact test failed to demonstrate a significant correlation between pathologically confirmed tumor extirpation and outcome.

Follow-up for the entire group of 20 patients ranged from 4 to 164 months, with a mean of 31 months. Four patients were alive with no evidence of disease at a mean of 68 months from diagnosis. One of these (no. 13), however, has experienced two local recurrences. The first of these occurred at 13 months postoperatively and involved the maxillary sinus and pterygopalatine fossa, and was treated with local resection through a transantral approach. The second occurred at 18 months and involved the medial canthus. This necessitated a superomedial maxillectomy and orbital dissection. At last follow-up he was without evidence of disease but obviously at high risk for recurrence.

Three patients were alive with disease at the time of last follow-up at a mean of 66 months from diagnosis. Thirteen patients died of disease at a mean of 20 months from diagnosis. Patterns of failure could not be reliably determined for the entire cohort, because patients treated palliatively were sometimes discharged to the care of local physicians. Palliation was reasonably effective, with 4 of 8

TABLE I.
Patients Diagnosed and Treated for SNUC at the University of Virginia Between 1991 and 2000 (1–15) and 1986–1991 (16–20).

No.	Age (y)	Stage	XRT (cGy)	Chemotherapy	Surgery	Pathology†	Margins	Status	Survival (mo)
1	66	C	5000	VP-16/Cisplatin	CFR	+	Close	DOD	25
2	38	C	5000	CAV, VP-16/Cisplatin	CFR	+	Positive	DOD	6
3	48	B	5000	CAV	CFR	–	N/A	DOD	19
4	62	C	6000	None	None	N/A	N/A	DOD	20
5	31	C	5000	CAV	CFR	+	Gross	DOD	10
6	41	C	5400	VP-16/Carboplatin	CFR	+	Close	DOD	12
7	82	C	6000	None	None	N/A	N/A	DOD	10
8	57	B	Yes*	None	Maxillectomy	Unknown	Unknown	AWD	54
9	38	C	5500	Cisplatin/5-FU	None	N/A	N/A	AWD	4
10	67	C	5040	CAV	CFR	–	N/A	NED	49
11	81	B	6000	None	None	N/A	N/A	DOD	19
12	60	C	Yes*	CAV	None	N/A	N/A	DOD	25
13	61	C	5040	CAV, VP-16/Cisplatin	CFR	+	Clear	NED	24
14	69	B	5000	CAV	CFR	–	N/A	NED	36
15	66	C	6330	CAV	None	N/A	N/A	DOD	9
16	71	C	5000	CAV	None	N/A	N/A	DOD	7
17	70	C	6500	CAV	None	N/A	N/A	AWD	114
18	67	C	5500	CAV	CFR	+	Close	NED	164
19	35	C	None	CAV	None	N/A	N/A	DOD	8
20	57	C	5000	CAV	CFR	+	Clear	DOD	97

*Final dose unknown (see text).
†Presence (+) or absence (–) of apparently viable tumor in the surgical specimen.
DOD = dead of disease; AWD = alive with disease; NED = no evidence of disease.

patients surviving longer than 1 year from diagnosis. Among the patients treated surgically, all of whom had adequate follow-up, there were 4 patients with local recurrences at a mean of 27.5 months, 3 with distant metastases at a mean of 9 months, and 3 with regional recurrences at 15 months. In addition, 2 of the patients who recurred locally experienced a second local recurrence after revision CFR at a mean of 6 months. Sites of distant metastasis included liver in 2 patients, bone in 2 patients, and lungs and dura in 1 patient each. All patients who developed disseminated disease recurred at multiple sites. Mean survival after distant metastasis was 3 months. It is noteworthy that 1 patient (no. 18) who developed a regional recurrence 3 months after CFR was salvaged with a neck dissection and is now a long-term survivor.

For the purposes of survival analysis, one patient (no. 9) from the 1991–2000 group was censored as a result of insufficient follow-up. Actuarial 2-year survival for all 19 evaluable patients was 47%. Kaplan-Meier survival curves with 95% confidence intervals for the 1986–2000 period is shown in Figure 2. Analysis of outcomes by clinical stage was not attempted because of an insufficient number of patients in the Kadish B group.

For the entire group of 19 patients, 10 underwent CFR as a part of their initial treatment. The mean survival of this group was 44 months, with a 64% actuarial 2-year survival. In the group treated without CFR, the mean survival was 30 months with a 25% actuarial 2-year survival. Kaplan-Meier survival curves for the entire group and after stratification by treatment type (CFR vs. no CFR) are shown in Figure 3. Comparison by treatment type using the log-rank test demonstrated a trend toward improved outcome in the group that underwent CFR (P = .076)

DISCUSSION

Since first identified as a discrete entity in 1986, approximately 50 cases of SNUC have been reported in the English language literature. The purpose of this report is to summarize our most recent 10-year experience with this neoplasm. When combined with two previous reports and additional follow-up from the group of patients diagnosed between 1986 and 1991, we have now reported long-term follow-up on 30 patients with SNUC. Several fundamental principles that warrant emphasis have emerged from this experience.

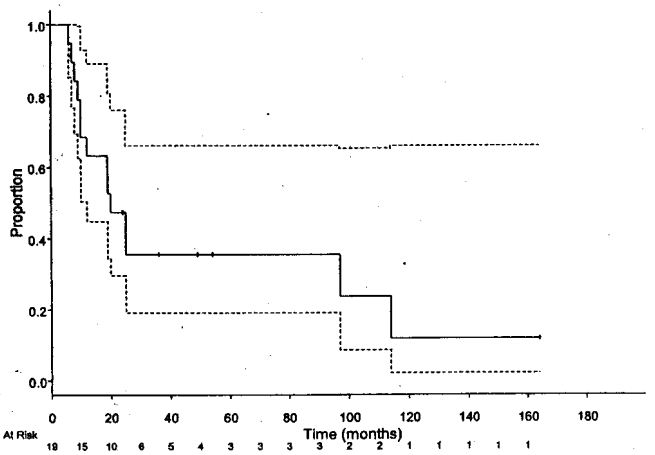

Fig. 2. Overall survival with 95% confidence intervals (1986–2000).

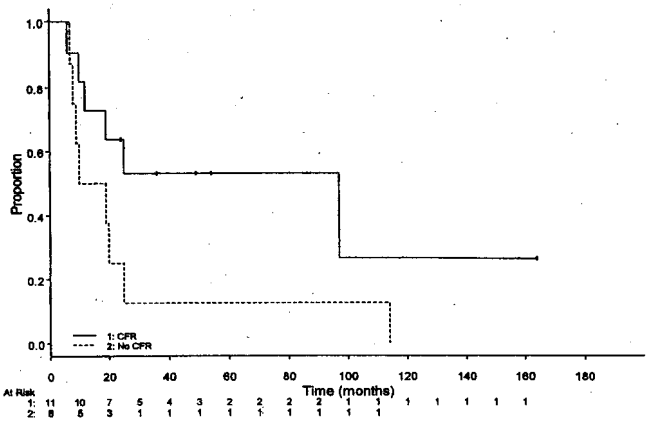

Fig. 3. Overall survival stratified by treatment modality (1986–2000).

First, as with many sinonasal tumors, patients often present with relatively advanced local disease. The majority of patients (73%) presented with Kadish C disease. This is similar to the proportion of stage C patients reported by Miyamoto et al.[5] The high prevalence of advanced disease likely reflects several characteristics of SNUC, including rapid growth, a propensity for invasion and destruction of local structures, and the potential for prolonged latency between development of the tumor and the onset of symptoms. Significant delay in diagnosis, which is sometimes implicated in contributing to locally advanced disease in other sinonasal tumors, was not clearly demonstrated in this cohort of patients. This may be related to the rapid growth of SNUC compared with lower-grade neoplasms, which may cause a more insidious onset of symptoms. Furthermore, patients with SNUC and other high-grade sinonasal tumors have a high incidence of epistaxis or bloody rhinorrhea and ocular symptoms, which are more likely to prompt diagnostic imaging or referral to an otolaryngologist.

Determination of treatment is predicated on accurate staging, which involves high-resolution axial and coronal computed tomography scans with contrast. If there is any suspicion of orbital or intracranial involvement, this should be confirmed by magnetic resonance imaging (MRI).[6] For patients who are marginal surgical candidates at the time of diagnosis, MRI is repeated at the conclusion of radiotherapy.

In general, non-surgical treatment is palliative. However, patients treated with chemoradiotherapy only may enjoy surprisingly long remissions, as demonstrated by one of the patients in the earlier time period who was alive with disease at last follow-up at 46 months and who is known to have survived to 114 months. All patients with good performance status and no evidence of distant or locally advanced disease, as defined below, are offered treatment for cure. At the University of Virginia, this initially involves three cycles of CAV and radiotherapy to a dose of 5000 cGy. Patients with a cardiac contraindica-

tion for doxorubicin may have this agent omitted. A poor clinical response to CAV may warrant a change in the regimen or beginning radiotherapy earlier than planned. Review of the literature reveals no systematic comparison of different chemotherapeutic regimens for SNUC, including CAV. Furthermore, the data presented here suggest that CAV-based neoadjuvant therapy will achieve tumor sterilization in a minority of cases, as only 3 of 8 patients who underwent surgical resection after being treated with this regimen had a complete pathologic response. Additionally, no conclusions between degree of response to neoadjuvant therapy and outcome could be made, because the former was not systematically determined, either clinically or radiographically, in this group of patients. In the absence of a prospective, randomized trial demonstrating the superiority of another regimen, however, we continue to advocate initial treatment with CAV based on anecdotal evidence suggesting its efficacy.

Surgery is performed between 1 and 2 months after the conclusion of radiotherapy. This has typically meant CFR, reflecting the high prevalence of ethmoid sinus and superior nasal vault disease, resecting the area occupied by the tumor before neoadjuvant therapy. The validity of this approach is supported by the observation that chemoradiotherapy alone would leave viable tumor in the majority of our cases, and by the observation that 2 patients in this series have no evidence of disease at 24 and 164 months after surgery despite the persistence of viable tumor after neoadjuvant therapy. In the future, more effective non-surgical treatment and novel imaging modalities capable of discerning residual tumor may render CFR obsolete, but presently all evidence suggests that an incomplete response to chemoradiotherapy should be presumed until proven otherwise by the analysis of a surgical specimen. Because previous reports from this institution demonstrated poor outcomes with non-surgical treatment,[2] we will continue to include CFR in our treatment algorithm until analysis of the results, either in terms of clinical outcomes or pathologic confirmation of tumor extirpation after chemoradiotherapy, suggests a shift in treatment philosophy.

Exclusion criteria for resection are involvement of the cavernous sinus, orbital apex, brain, or extensive disease in the infratemporal fossa. In the case of periorbital involvement, the periorbita should be removed en bloc with the specimen based on gross appearance. Once the specimen is removed, additional margins are taken and sent for frozen section analysis. Only in the rare case of otherwise resectable disease with extension into the orbital fat do we consider performing an orbital exenteration. By this criterion, no patient in this series required an exenteration. We favor a lateral rhinotomy to approach the tumor from below, but recognize that others have suggested alternative approaches, including midface degloving[7] and the subcranial approach.[8] If the lateral rhinotomy incision is made midway between the nasal dorsum and nasofacial groove, respecting the esthetic subunits of the nose, an acceptable cosmetic result is obtained.

Despite aggressive treatment, most patients with SNUC will not be cured of their disease. Of the 10 patients who underwent surgical resection, only 2 have had no recurrences. Analysis of patterns of failure reveals an approximately equal number of local, regional, and distant recurrences. Virtually all failures manifested within 2 years of surgery. The sole exception was a local recurrence in patient no. 20 67 months after CFR and 24 months after neck dissection for a regional recurrence. This patient had been initially diagnosed as having esthesioneuroblastoma, perhaps indicating that his tumor was of a less aggressive histologic subtype. In general, patients who have been continuously free of disease at 24 months are likely to be cured, although continued close follow-up is advised.

Our results show a 47% overall 2-year survival rate and 64% 2-year survival rate for patients who underwent CFR. The superior outcome in the latter group is likely reflective of several factors, including selection bias in favor of less advanced local disease and the efficacy of CFR in eliminating viable tumor after neoadjuvant therapy. These results compare favorably to other published series. Miyamoto et al.,[5] in the only other series incorporating more than 10 patients, reported a 42% overall 2-year survival rate. Gorelick et al.[9] reported on 4 patients treated with chemoradiotherapy followed by CFR through a subcranial approach. Only one of these patients survived longer than 24 months and was alive with intracranial disease at the time of last follow-up. Smith et al.,[10] in a comparison of SNUC and sinonasal neuroendocrine carcinoma, reported 6 patients with SNUC who had been treated with surgical resection and postoperative radiotherapy. Only 1 of these patients had died, and 2 had no evidence of disease. However, mean follow-up was less than 12 months.

CONCLUSION

Treatment of SNUC continues to present a challenge that requires a multidisciplinary approach, including otolaryngology–head and neck surgery, neurosurgery, ophthalmology, radiation oncology, and medical oncology. The cornerstone of surgical treatment is CFR, although in theory patients with disease confined to the maxillary sinus and adjacent lateral nasal wall may be effectively treated with maxillectomy. Despite the generally grim prognosis, some patients will be cured and most will enjoy prolongation of life with minimal treatment-related morbidity with aggressive, multimodality therapy.

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