Esthesioneuroblastoma: clinical presentation, radiological, and pathological features, treatment, review of the literature, and the University of Virginia experience

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Esthesioneuroblastoma is a rare and malignant upper nasal cavity neoplasm involving the anterior skull base. Treatment includes surgery, radiotherapy, chemotherapy, or a combination. The ideal treatment modality has yet to be determined. Esthesioneuroblastoma often lies in proximity to the optic nerves, optic chiasm, and the orbit. Resection risks damaging these critical structures, and radiotherapeutic techniques, similar to those applied for paranasal sinus tumors, may damage these vital structures and result in late sequelae such as blindness and cortical necrosis.

Management strategies for this neoplasm lack uniformity, and there is no universally accepted staging system. In this paper the authors discuss the clinical presentation, radiological and pathological features, and treatment of this rare, malignant skull base neoplasm, as well as review the literature. They also present their results and treatment regimen, which includes preoperative radio- and chemotherapy or 1) craniofacial resection if the lesion has a significant intracerebral component, or 2) frontal sinus resection if little intracranial extension exists.

KEY WORDS • esthesioneuroblastoma • radiation therapy • chemotherapy • skull base tumor

Since the original papers, numerous studies have been published, in each of which the patient population was limited and the treatment regimens multiple. Although the data reported in these studies have been of great interest over the years, the clinical and scientific merits have been diminished because of the small population sizes and the varied treatment protocols.

CLINICAL PRESENTATION

Because sinonasal malignant lesions are rare and difficult to distinguish from their benign counterparts, their diagnosis is challenging. These similarities between benign and malignant lesions at initial presentation may lead to a significant delay in the diagnosis of malignancy. Given the absence of classic symptoms, patients are often not examined until they present with nasal obstruction, headache, nasal pain, excessive lacrimation, epistaxis, anosmia, and visual changes. The most common complaint is longstanding unilateral nasal obstruction that has been present for months, sometimes years, before presentation.

The disease is initially demonstrated with a bimodal age distribution; it peaks first between age 10 and 20 years and later between age 50 and 60 years, and is slightly more common in females. The tumor can spread submucosally...
in all directions, thereby involving the parasal sinuses, nasal cavity, and surrounding structures. These lesions can cross the cribiform plate and invade the brain or seed the cerebrospinal fluid. Such lesions often require resection via a craniofacial approach. This uncommon neoplasm is locally aggressive and can metastasize by lymphatic and hematogenic routes. Esthesioneuroblastoma is an aggressive malignant tumor derived from the specialized neuroepithelium of the upper nasal cavity; it accounts for 3% of all endonasal neoplasms. In cases of metastatic disease, 20 to 30% will involve the CNS. In these cases the neoplasm invades the CNS by growing through the cribiform plate and invading the anterior cranial base. When it has entered the CNS, esthesioneuroblastoma metastasizes to either the brain parenchyma or leptomeninges.

RADIOLOGICAL FEATURES

Contrast-enhanced axial and direct coronal CT scanning is performed in all patients to obtain all necessary preoperative information, such as proximity to the adjacent sinuses, in Kadish Stage A or Stage B tumors (Table 1). The protocols for CT scanning must include axial and coronal scans of 1- to 5-mm-thick slices with intravenous contrast. Esthesioneuroblastomas are solid and enhancing nasal cavity masses that may manifest erosion into nearby osseous structures of the orbital plate of the ethmoid bone, cribiform plate, and fovea ethmoidalis (Fig. 1). In cases in which CT scanning reveals nasal roof erosion evidence of intracranial extension, we also recommend acquiring MR images because they provide a more sensitive assessment for unrecognized intracranial lesions. Intraluminal calcification observed on neuroimaging can be considered pathognomonic for esthesioneuroblastoma, and the presence of cysts along the intracranial margins of Kadish Stage C lesions in which there is intracranial extension also yields a definitive diagnosis.

In Kadish Stage C disease, it is important to perform T₁-weighted gadolinium-enhanced MR imaging to obtain essential additional information, particularly when walls of the bones are thinned or eroded. Fat-suppression T₁-weighted imaging visualizes the tumor more clearly. On T₁-weighted MR images esthesioneuroblastomas present as homogeneously enhancing tumors with intermediate signal intensity, whereas on T₂-weighted images the original intensity is increased. Occasionally in cases in which there is intracranial extension tumor, cysts at the tumor margins are also present. The main advantage of an MR imaging is its ability to delineate intraorbital and intracerebral extension. The tumor appears as hypointense to gray matter on T₁-weighted images and isointense or hyperintense to gray matter on T₂-weighted images. Multiplanar T₁-weighted MR images provide excellent contrast between the very high–intensity signal present after sinus fluid or mucosa obstruction and the intermediate–intensity signal of the adjacent tumor.

In assessing CT and MR imaging studies, it is sometimes difficult to determine whether the dura is invaded by tumor. Because of the thin fovea and cribiform complex, the dura is often the significant barrier to tumor penetration into the brain. Notwithstanding both neuroimaging studies, it may not be certain that the dura is involved until surgery. As a result, the team must be prepared to resect dura and replace it with autogenous fascia, temporalis, or fascia lata, for example, when performing craniofacial resection. Computerized tomography and MR imaging are complementary examinations performed preoperatively to define the extent of tumor, staging, and surgical approach. The primary advantage of CT studies is that they allow the team to evaluate osseous involvement around the nasal septum, orbit, and anterior skull base.

PATHOLOGICAL CHARACTERISTICS

Since its first descriptions, the histogenesis of this neoplasm has been of debate. This controversy has given rise to a variety of names including esthesioneuroblastoma, olfactory neuroepithelioma, olfactory neuroblastoma, and others. Several anatomical origins of esthesioneuroblastoma have been suggested, including the sympathetic fibers of the anterior nasal cavity, the neuroectodermal cells of the sphenopalatine ganglion, the olfactory placode, and the vomeronasal organ. Several studies have confirmed, however, that the histological subtype has no bearing on clinical behavior or prognosis. In summary, a diagnosis of esthesioneuroblastoma is made based on gene expression at a molecular level have not correlated with clinical outcomes.

Esthesioneuroblastomas are thought to arise from cells of the olfactory epithelium. These malignant cells are mitotically active and are precursor cells that give rise to sustentacular and neuronal cells. On high-power microscopic examination they are shown to have a vascular stroma with fibrovascular components and pseudorosettes (Fig. 2). The tumor is histologically similar to malignant lesions of the sympathetic ganglia, adrenal medulla, and the retina. Common features are small, round neuroepithelial cells arranged in rosette or pseudorosette patterns, separated by fibrous elements. Rosettes consist of a central space rimmed by columnar cells with radially oriented nuclei. In the past considerable effort was expended to define histological subtypes. The authors of numerous studies have confirmed, however, that the histological subtype has no bearing on clinical behavior or prognosis. Immunohistochemical and histological examinations show that esthesioneuroblastoma is of neuroendocrine cell origin and that a broad panel of antibody agents is necessary to verify the diagnosis. A neuritic derivation is indicated ultrastructurally by the presence of dense neurosecretory granules and neuritic processes within tumor cells. In summary, a diagnosis of esthesioneuroblastoma is made.
mas is determined using a combination of factors, including light microscopic appearance, and a battery of immunohistochemical stains, (chromogranin, synaptophysin, S-100 protein, and neuron-specific enolase).23

Genetic and Molecular Analysis

Developmental biologists have shown that the human equivalent of HASH-1, a marker expressed in the immature Drosophila fly olfactory neurons, was expressed in six primary and one metastatic specimens of esthesioneuroblastoma; the olfactory master protein, a protein expressed in mature olfactory neurons only, was not. Based on the results of this study, the authors suggested that esthesioneuroblastoma might develop from immature, rather than mature, olfactory neurons.8

The authors of genetic and molecular studies have shown that esthesioneuroblastoma is a member of the Ewing sarcoma and PNET family. The translocation commonly seen in Ewing sarcoma and PNETs (EWS/FLI1 genes) has been confirmed in esthesioneuroblastoma cell lines.68 Alterations of chromosome 1 in pPNETs have been described. Ninety-five percent of pPNETs show chromosomal translocations that are considered specific for this class of tumor [t(11;22)(q24;q12) or t(21;22) (q22;q12)], and these translocations fuse a portion of the EWS gene on chromosome 22 to either of the two Ets family transcription factors [FLI1 on 11q24 (5, 6) or ERG on 21q22].68 Consequently, these fusion genes express chimeric proteins capable of cell transformation and act as aberrant transcription factors.27,51 Identification of fusion transcripts [EWSyFLI1 and EWSyERG] with reverse-transcription polymerase chain reaction has formed the basis a sensitive and specific diagnostic test for pPNETs.

TREATMENT OF ESTHESIONEUROBLASTOMA

The importance of staging the extent of disease in malignant neoplasms has long been recognized because the stage usually correlates with prognosis.16,17,26 Establishing a histopathological diagnosis is essential before initiating treatment for esthesioneuroblastoma. A biopsy specimen should not be obtained until all neuroimaging studies have been performed to avoid swelling effects and the inadvertent biopsy sampling of other nasal tumors of neurogenic origin.

Multimodality treatments are the most frequently advocated interventions, and craniofacial resection is the most common therapy. Craniofacial resection has evolved into the best surgical procedure for achieving safe, en bloc resection of disease.35,37–40 In 1959 with treatment focused on surgery as the primary modality and with the knowledge that the incidence of tumor recurrence was significant, Malecki41 described for the first time the concept of the en bloc resection, rather than fragmented excision, of tumors of the superior nasal vault with adequate margins. Despite this report, however, it was not until the 1970s that Ketcham, et al.,33 and then Clifford9 popularized craniofacial resection in which the cribiform plate was removed to prevent the perineural extension of the tumor to the frontal lobes along the olfactory rootlets. In the 1970s at our institution, the senior author, (J.A.J.) and his colleague G. S. Fitz-Hugh, M.D. in the Department of Otolaryngology–Head and Neck Surgery, began to advocate a multidisciplinary craniofacial approach and resection; in this procedure the goal was to obtain an en bloc resection, and the emphasis was on a team approach.19,35,37–40 In one study the disease-free survival rate improved from 37.5 to 82% when extracranial excision and craniofacial resection were compared.37–39

SURGERY-RELATED NUANCES AND COMPLICATIONS

Endocranial extension and the close relationship to the ethmoid roof and cribiform plate require a combined transfacial and neurosurgical approach. A craniotomy is probably not justified for tumors classified as T1 by Biller, et al., (Table 2) in which there is clear radiological evidence of a normal cribiform plate and upper ethmoid
cells exist. All other patients should undergo a transfacial approach combined with a bifrontal craniotomy. A craniofacial resection permits en bloc resection of the tumor, better visualization of any intracranial extension, and protection of the brain and optic nerves. The resection should include the entire cribriform plate and crista galli (Fig. 3).

The postoperative complications are infections, including abscess surrounding the flap and, less commonly, subdural or epidural abscesses. The closure of the anterior skull base is difficult and not always watertight. As a result, meningitis can develop in some patients if there is a skull base defect and resultant CSF leak with the need for repair. Postoperative development of pneumocephalus can also occur with resultant brain compression. Blindness secondary to optic nerve injury as well as either intracerebral bleeding or internal carotid artery injury, are exceptional but serious complications. Radiotherapy-related complications also are rare and include necrosis of the bone flap, retinopathy, postirradiation cataracts, and vision loss. Delayed complications include necrosis of the frontal bone flap, lacrimal drainage obstruction, and frontal sinus mucoceles.

Some surgeons have prevented pneumocephalus in the immediate postoperative period by using a nasal trumpet in the ipsilateral nasal fossa and nasal packing to divert pressurized air. The cranial floor is repaired using various techniques, such as a pericranial flap, temporalis muscle, and fascia transposition, or a layer of fascia lata held with fibrin glue. These procedures have prevented the herniation of cranial contents into the nasal cavity and minimized the incidence of CSF leakage.

In a series recently reported by our group, nine (25.7%) of 35 patients suffered central nervous system complications. These included one case of elevated intracranial pressure, two of pneumocephalus that required decompressive surgery, one of a cerebrovascular accident that caused a temporary left hemiplegia, which completely resolved, and five of CSF leaks, four of which were treated satisfactorily with lumbar peritoneal shunts and one of which required no therapy.

In eight (22.9%) of the 35 patients orbital complications were secondary to therapy. Three developed epiphora, two radiation-induced cataracts, one radiation-induced keratitis, and two developed transient diplopia secondary to fourth cranial nerve dysfunction. Seven (20%) of the 35 patients suffered systemic complications that were not life threatening (hyponatremia, diabetes insipidus, wound seroma, pulmonary embolus, hypothyroidism, amenorrhea, and prolactinoma) and for which they received treatment.

In 22 cases the tumors were Stage C, and the patients therefore underwent chemotherapy; chemotoxicity resulted in (18.2%): one patient who suffered a myocardial infarction, one who developed bilateral vocal cord palsies, one who suffered peripheral neuropathy, and one who developed herpes zoster during his chemotherapy treatment. Only three patients (8.6%) developed infectious complications postoperatively. In two patients infected bone flaps occurred, requiring removal, and in one patient an epidural abscess developed, necessitating surgical drainage. There were no cases of meningitis. Cosmetic complications developed in five patients (14.3%): a saddle-nose deformity that necessitated a calvarial bone graft in one case, a nasocutaneous fistula in one case, resorbed frontal bone flaps in two cases, and enophthalmos secondary to radiotherapy in the fifth case.
ADJUVANT THERAPY

The use of radiotherapy as the only intervention in cases of esthesioneuroblastoma was originally described by Berger, et al.3 In the subsequent years surgical treatment became more prevalent and was often undertaken as the sole treatment for these neoplasms. In a study from the Mayo Clinic the authors reported that there was no difference in survival rates between patients treated with surgery and those with radiotherapy.20 In other studies authors have also shown that an increase in local tumor control was achieved by combining pre- and postoperative radiotherapy.69,70 The local tumor control rates were between 44% and 86% for surgery alone, whereas surgery combined with radiotherapy resulted in reduced local failures of 0 to 40%.15,18,20,31 Adjuvant radiotherapy is thought to augment surgical 5-year cure rates from 10 to 15%; the 5-year survival rate for radiotherapy alone is reported to be 23%; whereas for surgery combined with radiotherapy it is 44%.32 In light of these results, our treatment protocol has evolved from one of excision to multimodality treatment. The use of palliative high-dose irradiation alone for unresectable disease yields a 5-year survival rate of 10 to 15%.66 Therefore, radiotherapy alone as a primary treatment modality is no longer a recommended option except for palliation in patients with advanced disease.46

In 1998 Polin and colleagues54 reported that patients at the UVA exhibited a significant response to adjuvant therapy with or without chemotherapy. Moreover, they found that in patients in whom a response to adjuvant therapy was demonstrated preoperatively there was a statistically significant chance of being disease free.

CHEMOTHERAPEUTIC TREATMENT

The role of chemotherapy in the management of patients with esthesioneuroblastoma is continually evolving.48 Our philosophy in treating patients with Kadish Stage C tumors is based on the principle that these tumors share certain biological characteristics with other chemosensitive tumors of neural crest origin (for example, neuroblastomas, high-grade neuroendocrine carcinomas, and PNETs).4 In 1990 Goldsweig and Sundaresan22 reviewed 25 cases reported in the literature and found improvement in 19 of the 20 patients in whom chemotherapy alone was undertaken for recurrence or metastatic disease.22 The most commonly used regimen includes cyclophosphamide with vincristine. Since 1981, patients with Kadish Stage C tumors have undergone preoperative chemotherapy at our institution. Cyclophosphamide (650 mg/m²) and vincristine (1.5 mg/m² with a maximum dose of 2 mg) were given every 3 weeks for a total of six cycles. Esthesioneuroblastomas are chemosensitive tumors. Treatment of Stage C disease is warranted, and multimodality therapy is reasonable in patients with metastatic disease.

REVIEW OF PUBLISHED SERIES

Skolnick, et al.,65 reported in a series of 50 patients in whom 5-year follow up was obtained. The 5-year survival rates were 64% for patients treated with surgery alone, 38% for those who underwent radiotherapy alone, and 50% for those who received combined therapy; the local recurrence rate was 48%. The other report of significance was published by Elkon, et al.,18 in 1979. Theirs was both a follow up to the report by Skolnick, et al., and a review of an additional 76 cases described in the literature between 1967 and 1977. They concluded that there was no advantage to multimodality therapy in the management of
early disease and that although treatment of advanced disease provided palliation a cure did not occur. Homzie and Elkon surveyed the world literature and excluded some cases because they lacked the necessary information to evaluate their prognostic variables and 11 cases because adequate follow-up data were not available. The authors determined that the cure rate for patients treated after 1966 was 64%, whereas that for those treated before 1966 was 23%. These data suggested that the changes in treatment patterns ultimately affected cure rate and that those patients who survived for at least 36 months had an excellent chance of reaching the 5-year survival mark.

Traditionally, esthesioneuroblastoma is staged, as suggested by Kadish. These authors divided the lesions into three stages: Stage A in which the tumor is limited to the nasal fossa; Stage B in which the tumor extends to the paranasal sinuses; and Stage C in which the tumor extends beyond the paranasal sinuses (Table 1). Currently, there are no epidemiological, molecular, or pathological prognostic indicators that are more valuable in predicting recurrence of disease or biological behavior than the Kadish staging system. The main shortcoming of the Kadish classification is that the language of defining Stage C is too broad. Recognizing these inadequacies, a proposed classification is based on the TNM system, which is predicated on CT and MR imaging findings. The study of esthesioneuroblastoma has clearly suffered from a uniform, effective staging system. Two other staging systems, the Biller method and the Dulguerov method, have also been described. In 1992 Dulguerov and Calcaterra criticized the Biller staging system (Table 2) because cribriform plate involvement was assumed in all cases and because craniotomy was required for accurate staging. As a result, they proposed a modified TNM system based on CT and/or MR imaging findings (Table 3).

Morita, et al., published a series of 49 patients treated at the Mayo Clinic over a 39-year period; they performed numerous treatment techniques that evolved over this long evaluation period. In seeking to determine prognostic factors, they found that the pathological grading system proposed by Hyams (Table 4) provided a statistically significant method of predicting outcome compared with the Kadish staging system.

Treatment results reported in the past were most likely flawed, probably by the inclusion of cases of sinonasal undifferentiated and neuroendocrine carcinoma (aggressive diseases associated with poor survival). In recent series, the 5-year survival rate has varied from 50 to 80%, with most studies indicating survival rates of greater than 70%. The Kadish system has a definitive prognostic value, and in patients harboring Stages A and B tumors, the 5-year survival rate appears to be 86%, whereas in those with Stage C tumors the 5-year survival rate appears to be 72%. The most frequent recurrence is local, with rates ranging from 20 to 40%. Although distant metastasis is not frequent (8%), it carries a very poor prognosis, and the presence of palpable lymph nodes is the most important prognostic factor for survival (for example, the 5-year survival is 0% in cases in which nodes are present and 65% in those in which they are not). In studies from the Mayo Clinic the authors emphasize that the Hyams histopathological grade is the most important prognostic factor, even though the results of other studies as well ours have failed to confirm this (Table 4).

### THE UVA MULTIDISCIPLINARY APPROACH AND RESULTS

The treatment protocol undertaken in our patient population was the same as that previously reported by Levine, et al., in 1986 with use of the Kadish staging system. For all stages of disease (Kadish Stages A–C), a preoperative 50-Gy dose of radiation was delivered because esthesioneuroblastomas are proven to be radiosensitive and because preservation of the eye in sinonasal malignancies has been shown. In addition, patients harboring Kadish Stage C lesions, in whom the tumor extended into the orbit, or intracranially, or in whom cervical metastases were present, but not those with distant metastatic disease, chemotherapy was undertaken (cyclophosphamide and vincristine) prior to the radiotherapy, as previously described. As in other institutions in which superior nasal vault tumors are treated, a team including the otorhinolaryngologist–head and neck surgeon, neurosurgeon, neuropathologist, radiation oncologist, and hematologist–oncologist evaluated each patient and was instrumental in determining and delivering treatment.

Our belief is that the majority of Grade IV esthesioneuroblastomas, as described by Hyams, can also be classified as sinonasal undifferentiated carcinomas. Because...
of the considerably more aggressive clinical behavior of the sinonasal undifferentiated carcinoma, the outcomes of this grading analysis can be affected.

A retrospective analysis of the medical records obtained in patients treated at our institution between September 1976 and May 1998 was performed. Although additional patients were evaluated and treated at our institution prior to this date, September 1976 reflects the time at which we introduced craniofacial resection as the standard surgical therapy for superior nasal vault tumors. In a cohort of 45 patients, 10 were excluded because surgery had not been performed at our institution. The remaining 35 patients were found to have completed definitive curative therapy performed at our institution. The remaining 35 patients were evaluated and treated at our institution prior to this date, September 1976 reflects the time at which we introduced craniofacial resection as the standard surgical therapy for superior nasal vault tumors. In a cohort of 45 patients, 10 were excluded because surgery had not been performed at our institution. The remaining 35 patients were found to have completed definitive curative therapy performed at our institution. The overall disease-free survival and total survival rates for these patients were calculated. Kaplan–Meier survival curves were estimated for the percentage of disease-free survival and total survival, which included cause-specific death, as well as death of nonesthesioneuroblastoma causes.

Of 19 patients with Grade II tumors, seven developed recurrent disease, and of five with Grade III tumors, four developed recurrences. Of the 19 Grade II tumors, there were six Stage B tumors and 13 Stage C; in two of the six patients harboring Grade II/Stage B tumors local recurrence/metastases developed, and in five of the 13 patients harboring Grade 2/Stage C lesions local recurrence/metastases developed. One of the Grade III/Stage B lesions recurred, and two of the four Grade III/Stage C lesions recurred as well. The one patient with a Grade I/Stage C lesion developed no additional disease. We were unable to correlate any clinical significance with this pathological grading system; however, we did find that the Kadish system was more clinically applicable, because the Stage C disease in both Grades II and III lesions was more clinically aggressive (Table 5).

Only two (6%) of the 35 patients in this series presented with cervical metastases, although in nine (25.7%) of 35 at least one episode of cervical metastasis occurred either prior to or after the completion of therapy. Of the seven in whom cervical disease developed following primary therapy, four sustained two to four episodes of cervical recurrences, despite surgical and adjuvant therapeutic intervention. This outcome is consistent with the data published by Davis and Weissler, who showed, by calculating the cumulative published data derived from the studies of 10 authors (total number of patients 207), that the ultimate cervical metastasis rate was 27% in this composite group. Also in this group of seven patients with delayed recurrent cervical disease, four (57%) of seven developed additional metastatic disease at a later date.

In five patients (14.3%) local recurrence developed a mean of 72 months (median 60 months) following definitive diagnosis, whereas in the other 10 (28.6%) delayed cervical or distant metastatic disease developed at one or more sites during their lives. In 37% of the patients at least one episode of metastatic disease eventually occurred. The longest duration before presentation with this first recurrence was 160 months.

Of those patients in whom delayed cervical metastases developed, the mean time following diagnosis of this occurrence was 84 months (range 42–124 months). Kaplan–Meier survival curves were estimated for the percentage of disease-free survival by month of follow up. The disease-free survival was 80.4% at 8 years, and the total survival (inclusive of all diseases for this patient group) was 75.2%.

There were five episodes of distant metastasis in four patients, and these occurred a mean of 33.3 months following diagnosis. In order of frequency the involved sites were bone, lung, and prostate. In one patient a radiation-induced primary squamous cell carcinoma developed 153 months after treatment, occurring in the contralateral inferior turbinate.

The mean follow-up period in these 35 patients was 95.7 months. The 80.4% 8-year disease-free survival rate proves the value of aggressive surgical therapy in conjunction with adjuvant therapy (radiotherapy with or without chemotherapy) in treating this malignant neoplasm. Of note 22 (62.9%) of the 35 patients presented with advanced Stage C disease. This 80.4% 8-year disease-free survival rate also includes 13 patients (37.1%) who developed metastatic disease (two at presentation and 11 in a delayed fashion).

The first metastases following completion of therapy was 74.8 months (range 10–160 months). In light of this, these patients require a longer follow-up period. In the studies published by Kadish and colleagues in 1976, only two patients with Stage C disease survived for 3 years or more. In our series, 22 (62.9%) of 35 patients presented with Stage C disease.

**CONCLUSIONS**

We believe that esthesioneuroblastoma can be a highly curable sinonasal malignancy, even in cases in which patients present with advanced disease. Our results and those of others indicate that surgery as well as adjuvant therapy should be recommended for the treatment of esthesioneuroblastoma. We also believe that preoperative radiotherapy can reduce the tumor burden, allowing a greater chance of gross-total resection. Adjuvant therapy should be considered in patients with advanced disease and unresectable disease. An extended follow-up period is required for these patients.

**TABLE 5**

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<th>Kadish Stage</th>
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