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### **Pediatric sinonasal neuroendocrine carcinoma following treatment for retinoblastoma. Human Pathology, 2009; 40:750-755.**

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Pediatric sinonasal neuroendocrine carcinoma following treatment for retinoblastoma. Human Pathology, 2009; 40:750-755 / A. Franchi; I. Sardi; V. Cetica; A.M. Buccoliero; F. Giordano; F. Mussa; L. Genitori; G. Oliveri; C. Miracco. - In: HUMAN PATHOLOGY. - ISSN 0046-8177. - STAMPA. - 40:(2009), pp. 750-755.

*Availability:*

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**Case study**

# Pediatric sinonasal neuroendocrine carcinoma after treatment of retinoblastoma

**Alessandro Franchi MD<sup>a,\*</sup>, Iacopo Sardi MD<sup>b</sup>, Valentina Cetica MD<sup>b</sup>,  
Annamaria Buccoliero MD<sup>a</sup>, Flavio Giordano MD<sup>c</sup>, Federico Mussa MD<sup>c</sup>,  
Lorenzo Genitori MD<sup>c</sup>, Giuseppe Oliveri MD<sup>d</sup>, Clelia Miracco MD<sup>e</sup>**

<sup>a</sup>Department of Human Pathology and Oncology, University of Florence, 50134 Florence, Italy

<sup>b</sup>Department of Pediatric Onco-hematology, University of Florence, 50134 Florence, Italy

<sup>c</sup>Department of Neurosurgery, “Anna Meyer” Hospital, Florence, Italy

<sup>d</sup>Department of Neurosurgery, Policlinico “Le Scotte,” Siena, Italy

<sup>e</sup>Department of Human Pathology and Oncology, University of Siena, Siena, Italy

Received 15 July 2008; revised 19 September 2008; accepted 23 September 2008

**Keywords:**

Retinoblastoma;  
Nasal cavity;  
Neuroendocrine  
carcinoma

**Summary** Patients who survive retinoblastoma are at risk for developing additional malignant neoplasms, including tumors of the sinonasal tract. We report 2 cases of secondary sinonasal malignancy arising in pediatric patients previously treated for retinoblastoma, with features of neuroendocrine carcinoma. Both lesions were characterized by a proliferation of round to oval cells arranged in solid sheets, trabeculae, and nests, diffusely infiltrating nasal mucosa and bone tissue. Immunohistochemically, they were diffusely positive for epithelial markers, as well as for neuroendocrine markers and for *TP53* and retinoblastoma gene products. *TP53* gene analysis showed the presence of a missense mutation P72R (CCC/CGC) and a single nucleotide polymorphism P36P (CCG/CCA) in exon 4 in 1 case. Literature review revealed 5 previously reported cases, all showing primitive undifferentiated morphology with variable expression of neural and epithelial markers. These tumors represent a peculiar subset of undifferentiated sinonasal neoplasms with extremely aggressive clinical behavior.

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**1. Introduction**

Patients who survive retinoblastoma (RB), particularly those affected by bilateral RB, are at risk for developing additional malignant neoplasms, including soft tissue sarcomas, osteosarcoma, melanoma, and brain tumors [1]. In addition, patients with RB are prone to develop nasal tumors possibly as an effect of radiation therapy [2,3]. Review of the literature, however, reveals that only a few examples of primary sinonasal malignancies arising in

patients with RB have been the object of detailed clinicopathologic analysis [4–7]. Most of these lesions had a primitive undifferentiated morphology with small round cell appearance and could fit in the Ewing sarcoma/PNET family, although definitive proof given by the identification of the specific t(11;22) is lacking [6,7]. Two cases reported by Frierson et al [4] were the object of extensive immunohistochemical analysis, demonstrating epithelial and neuroendocrine differentiation in one case and multidirectional differentiation with expression of epithelial, neural, and myogenic antigens in the other. Another case reported by Greger et al [5] had morphological and immunohistochemical features consistent with sinonasal

\* Corresponding author.

E-mail address: franchi@unifi.it (A. Franchi).

undifferentiated carcinoma (SNUC) and was characterized by a deletion of RB-1 locus that was not present in normal tissues, suggesting the involvement of this gene in the development of these tumors. Here we report 2 additional cases of secondary sinonasal malignancy arising in patients previously treated for RB, with ultrastructural, immunohistochemical, and molecular characterization.

## 2. Materials and methods

### 2.1. Immunohistochemistry

Paraffin sections (5- $\mu$ m thickness) were dewaxed, hydrated, and, after inactivation of endogenous peroxidase, immunostained using an automated labeled streptavidin-biotin-peroxidase method on the GenoMX i6000 immunostainer (Biogenex, San Ramon, CA). Table 1 reports the antibody source, dilution, and antigen retrieval protocols used.

### 2.2. Fluorescent in situ hybridization analysis for EWS gene rearrangement

Fluorescent in situ hybridization (FISH) analysis was conducted on paraffin sections using a commercially available break-apart dual-color probe for EWSR1 (22q12)

(Vysis; Abbott Laboratories, Des Plaines, IL) according to the manufacturer's recommendation. For each sample, a minimum of 200 nonoverlapping tumor cells were evaluated for the presence of fused (normal) or split (rearranged) signals.

### 2.3. TP53 gene sequencing

Polymerase chain reaction primers for exons 4 to 9 of TP53 gene were designed to obtain fragment of no more than 300 bp. Amplification reactions were performed with 100 ng of genomic DNA, 10 ng of each primer, 200  $\mu$ mol/L dNTPs, 1 $\times$  polymerase chain reaction buffer, and 2.5 U Taq polymerase in a final volume of 25  $\mu$ L. Polymerase chain reaction products were directly sequenced on both strands using an ABI PRISM 310 Genetic Analyzer (Perkin-Elmer Applied Biosystems, Foster City, CA).

## 3. Results

### 3.1. Case histories

#### 3.1.1. Case 1

The patient was diagnosed with bilateral sporadic RB at the age of 5 months. She underwent enucleation of the right eye, and 1 month later, the left eye was treated with

**Table 1** Features of the antibodies used in the study and results of the immunohistochemical staining

Antibody	Source	Titration	Antigen retrieval	Case 1	Case 2
CK AE1/AE3	Clone AE1/AE3 PCK26; Ventana, Tucson, AZ	Prediluted, 28 min, 37°C	Protease, 4 min	+ (diffuse)	+ (diffuse)
CK CAM5.2	Clone Cam 5.2; BD Biosciences, San Jose, CA	Prediluted, 20 min, 37°C	Protease, 4 min	+ (diffuse)	+ (diffuse)
CK 5/6	Clone D5/16 B4; Chemicon Int, Temecula, CA	1:60, 32 min 37°C	35 min MW citrate buffer, pH 6.0	+ (focal)	–
CK 7	Clone K72; Cell Marque Corp, Hot Springs, AR	Prediluted, 12 min, 37°C	30 min of cell conditioning 1	+ (focal)	+ (focal)
CK 14	Clone LL0022; Novocastra, Newcastle-upon-Tyne, UK	1:40, 60 min, RT	30 min of cell conditioning 1	–	–
EMA	Clone E29, Cell Marque Corp	Prediluted, 12 min, 37°C		+ (diffuse)	+ (diffuse)
NSE	Clone E27, Cell Marque Corp	Prediluted, 24 min, 37°C	35 min MW citrate buffer, pH 6.0	+	+
CD56	Clone 123C3.D5, Cell Marque Corp	Prediluted, 32 min, 37°C	30 min of cell conditioning 1	+ (focal)	+ (focal)
Chromogranin A	Clone LK2H10, Ventana	Prediluted, 32 min, 37°C	30 min of cell conditioning 1	+ (focal)	+ (focal)
Synaptophysin	Polyclonal rabbit, Cell Marque Corp	Prediluted, 32 min, 37°C	30 min of cell conditioning 1	+ (diffuse)	+ (focal)
Neurofilaments	Clone FNP7, DA2, RMd020.11; Zymed, San Francisco, CA	1:50, 24 min, 37°C	35 min MW citrate buffer, pH 6.0	–	–
S-100 protein	Polyclonal rabbit, Dako, Glostrup, Denmark	1:2000, 24 min, 37°C	Protease, 4 min	–	–
CD99	Clone H036-1.1, Ventana	Prediluted, 32 min, 37°C	30 min of cell conditioning 1	–	–
p53	Clone DO7, Dako, Glostrup, Denmark	1:40, 60 min, RT	30 min MW citrate buffer, pH 6.0	+ (diffuse)	+ (diffuse)
RB	Clone 13A10 Novocastra	1:30, 60 min, RT	35 min MW citrate buffer, pH 6.0	+ (diffuse)	+ (diffuse)

Abbreviations: CK, cytokeratin; NSE, neuronal specific enolase; RT, room temperature; MW, microwave oven.

radiotherapy (amount unknown). At the age of 15 years, she presented with paresthesia of the left side of the face, and after magnetic resonance imaging, a diagnosis of sphenoidal sinusitis was made. She was treated with antibiotic therapy, which led to regression of symptoms. Three months later, she presented with visual disturbances, and magnetic resonance imaging revealed a lesion occupying the left maxillary sinus, the ethmoidal cells, the sphenoid sinus, and the frontal sinus. The lesion infiltrated the nasal cavity bilaterally, the right maxillary sinus, the left orbit, and the left anterior cranial base, and also involved both frontal lobes. Computed tomography scan showed evidenced erosion of the left frontal and temporal bones, the pavement of the sphenoid sinus, the ethmoid bone, the wall of the left maxillary sinus, the nasal septum, and the hard palate. After incisional biopsy, the patient underwent surgical removal of the tumor through a frontobasal approach. The postoperative course was uneventful. Eighteen months after diagnosis, the patient had intracranial recurrence of the tumor leading to death.

### 3.1.2. Case 2

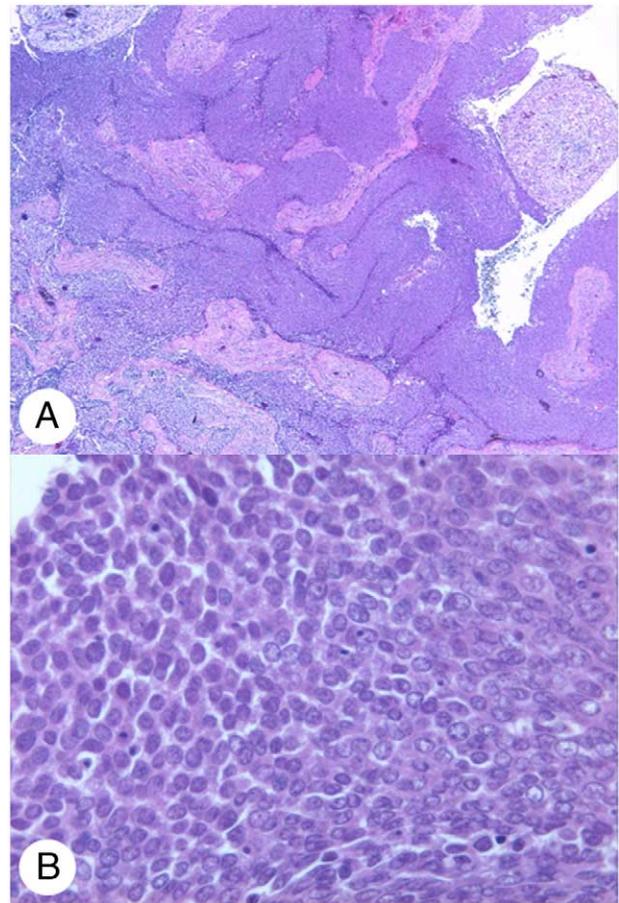
A male subject was treated for unilateral sporadic RB at the age of 20 months with enucleation of the right eye followed by radiotherapy (total dose, 40 Gy). After 148 months, at the age of 13 years, he experienced episodes of headache and vomiting. A computed tomography scan revealed a large mass centered in the ethmoid and involving the sphenoid, the superior and median choanae, the right nasal cavity, the right orbit, and the median cranial fossa. Treatment included surgery, followed by radiotherapy (total dose, 61.2 Gy) and chemotherapy. The patient was alive with disease at 36 months' follow-up.

## 4. Microscopic findings

Both tumors were composed of medium to large round to oval cells arranged in solid sheets, trabeculae, and nests, diffusely infiltrating nasal mucosa and bone tissue (Fig. 1). Neoplastic cells were closely packed and had scanty weakly eosinophilic cytoplasm and large nuclei with 1 or 2 small nucleoli (Fig. 1). Mitotic figures were numerous, as were apoptotic bodies. Areas of necrosis were seen particularly in case 1. The schneiderian epithelium did not show signs of dysplasia in any of the cases.

### 4.1. Immunohistochemistry

The immunohistochemical findings are summarized in Table 2 and illustrated in Fig. 2. Both cases showed diffuse expression of epithelial markers, including cytokeratins AE1/AE3 and CAM5.2, and EMA (epithelial membrane antigen). They also expressed neural markers such as neuronal specific enolase, chromogranin, synaptophysin, and CD56. Diffuse nuclear staining was observed for p53 and RB gene products.



**Fig. 1** (A) Low power view showing the sinonasal tumor of patient 1, which is composed of sheets and ribbons of uniform round cells with extensive areas of necrosis. (B) The neoplastic cells have indistinct cell membranes, scant cytoplasm, oval nucleus with fine chromatin, and inconspicuous nucleoli.

### 4.2. Electron microscopy

Material for ultrastructural analysis was available in case 1. The tumor was composed of closely packed cells joined by primitive junctions. The nucleus was round to oval, eccentrically placed, and contained a prominent nucleolus. The cytoplasm presented few organelles, including rough endoplasmic reticulum and free ribosomes, mitochondria, as well as bundles of tonofilaments. A few dense core granules were identified in the cytoplasm of neoplastic cells.

### 4.3. Fluorescent in situ hybridization analysis

No rearrangement of the EWS gene locus was documented by dual color FISH analysis.

## 5. TP53 gene sequencing

The analysis of exons 4 to 9 of *TP53* gene revealed 2 genetic alterations in the lesion of patient 2: a missense

**Table 2** Clinicopathologic features of sinonasal small round cell tumors developing in patients treated for bilateral RB

Reference	Age (y)	Sex	Time span from the treatment of RB and the diagnosis of the sinonasal tumor (y)	Diagnosis	Genetic analysis
6	23	M	22	SCUC	ND
	38	F	37	PNT with multilineage differentiation	
7	18	F	36	Undifferentiated sinonasal carcinoma	RB-1 locus deletion
8	19	F	18	Sinonasal PNT	No abnormalities
9	19	F	18	Sinonasal PNT	ND
Present case 1	15	F	15	NEC	
Present case 2	13	M	11	NEC	TP53 missense mutation and nucleotide polymorphism in exon 4

Abbreviations: M, male; F, female; SCUC, small cell undifferentiated carcinoma; PNT, primitive neuroectodermal tumor; NEC, neuroendocrine carcinoma; ND, not done.

mutation P72R (CCC/CGC) (Fig. 3) and a single nucleotide polymorphism P36P (CCG/CCA) in exon 4. No alteration of exons 4 to 9 of p53 gene was detected in patient 1.

## 6. Discussion

Patients affected by RB have a substantial risk for developing a second malignancy related to genetic predisposition, but it is likely that radiotherapy contributes to the significantly increased risks observed for cancers of the brain, nasal cavities, and orbit [2]. Indeed, bone and soft tissue tumors, particularly Ewing sarcoma and osteosarcoma, develop with relatively high frequency near the eyes, but the sinonasal tract can be affected as well by sarcomas, carcinomas, and a subset of poorly differentiated tumors with neuroectodermal features [8-10].

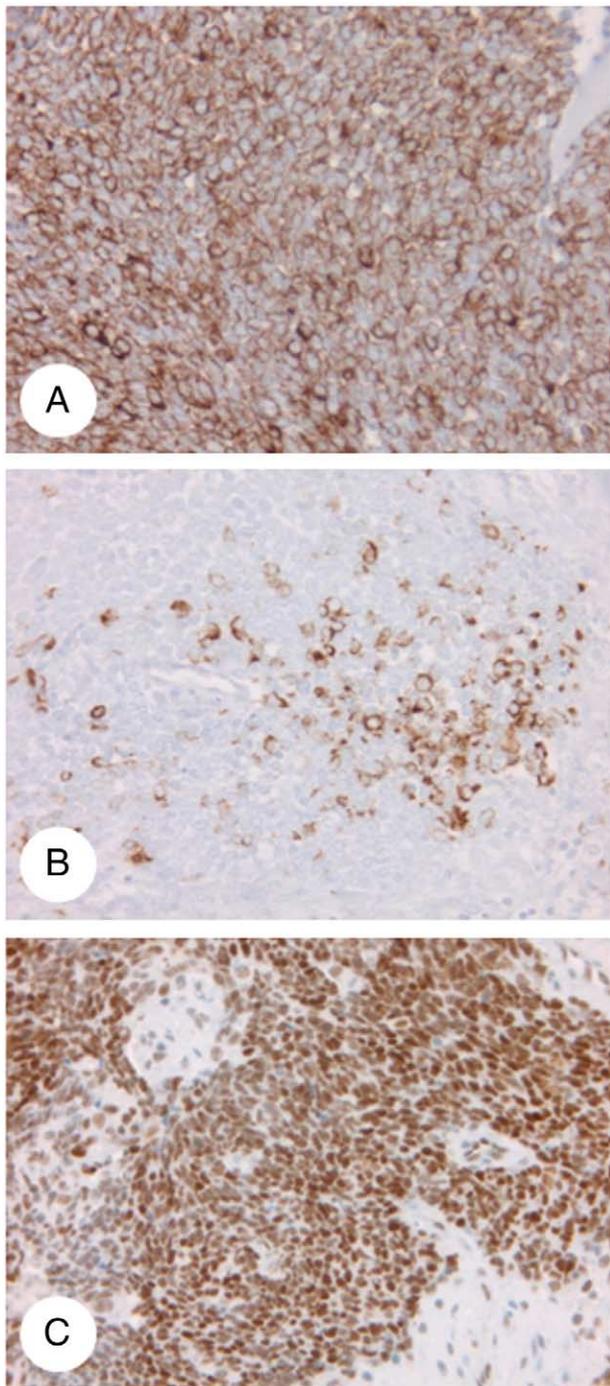
Here we report 2 pediatric patients previously treated for RB with surgery and irradiation who developed a second tumor in the sinonasal tract with features of a poorly differentiated carcinoma with neuroendocrine differentiation. Only few examples of these malignancies in this peculiar clinical setting have been previously reported [4-7]. Their clinicopathologic features are summarized in Table 2. Tumor developed in young adult patients, with a predominance for females, after an average of 26.2 years after treatment of RB, which included radiotherapy in all cases. Histologically, they were characterized by undifferentiated round cell morphology and putative neuroectodermal differentiation revealed by the presence of Homer Wright rosettes [4] and expression of neural markers, whereas epithelial differentiation has been less consistently documented [4-7].

Sinonasal round cell neoplasm with neuroectodermal differentiation may be further divided into tumors showing primarily epithelial differentiation (neuroendocrine carcinomas) and nonepithelial tumors, including olfactory neuroblastoma, Ewing sarcoma, and melanoma [11]. Olfactory

neuroblastoma can be considered in the differential diagnosis both for the histologic appearance of the 2 lesions and because of the involvement of the vault of the nasal cavity. Although olfactory neuroblastoma may occasionally show limited positivity for cytokeratins, this possibility can be excluded based on the diffuse expression of epithelial markers (cytokeratins and EMA), based on the absence of S-100 protein positive sustentacular cells, and for the ultrastructural features indicative of epithelial differentiation. Similarly, Ewing sarcoma and primary sinonasal melanoma can be ruled out based on the results of the immunohistochemical studies and FISH analysis documenting the absence of rearrangement of *EWS* gene.

The lesions presented herein, therefore, appear to belong to the spectrum of sinonasal neuroendocrine carcinomas. This is a rare and poorly defined group of tumors that may show morphological features overlapping with those of small cell neuroendocrine carcinoma of pulmonary and extra pulmonary origin [12]. Sinonasal neuroendocrine carcinoma is a highly aggressive neoplasm with frequent local relapse and a high rate of distant metastasis despite combined modality therapy [12]. Another tumor that may show varying degrees of neuroendocrine differentiation is SNUC. However, the present cases differ from SNUC, having a higher degree of neuroendocrine marker expression and strong p53 expression, which is rarely documented in SNUC [13].

In general, carcinomas of the upper aerodigestive tract are rare in children [14]. A distinctive subtype of poorly differentiated carcinoma characterized by a (15;19) chromosomal translocation may occur in the nasal cavities and nasopharynx of pediatric age patients [15]. Patients have no history of prior irradiation, and the lesion presents in an advanced stage and follows a rapidly fatal course despite aggressive multimodal therapies. Histologically, they present features of poorly differentiated squamous cell carcinoma, with no evidence of neuroendocrine differentiation either immunohistochemically or ultrastructurally [15].



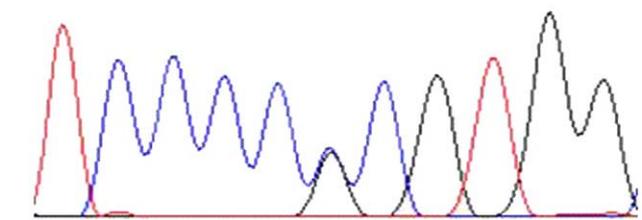
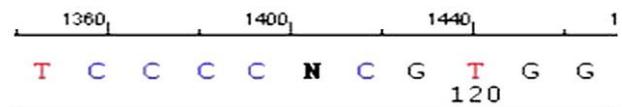
**Fig. 2** Results of the immunohistochemical staining. Neoplastic cells were positive for cytokeratins AE1/AE3 (A), chromogranin (B), and p53 (C).

The *TP53* tumor suppressor gene is the most common target of mutation in head and neck cancer, and therefore, we analyzed its status in both tumors. We found that one patient presented with the R72P polymorphism in exon 4, resulting in a substitution of Pro for Arg in the transactivation domain. This polymorphism has been extensively studied with regard to its possible involvement

in increased risk for cancer development, but results have been controversial. Although some authors have reported a correlation between the presence of Arg allele [16], as well as between homozygous proline [17] and development of carcinoma at different anatomic sites, this has not been confirmed in studies conducted on head and neck cancer [18,19]. However, the possible role of this polymorphism in the susceptibility to the development of second malignancies in patients treated for RB may deserve further investigation. The remaining p53 mutation was a single nucleotide substitution without amino acid change in exon 4 (CCG to CCA). It is possible that these polymorphisms could be responsible for enhanced cancer risk or, alternatively, that the p53 allele carrying the nucleotide substitution could be in linkage with other loci involved in controlling genomic stability [20].

The development of RB requires the inactivation of both alleles of the RB gene on chromosome 13, band 13q14. In the familial form of RB, patients carry a germline mutation of one allele, and the tumor develops after a somatic mutation occurs in the second allele. Analysis of the RB gene in sinonasal tumors occurring in patients with RB has led to conflicting results. Although Greger et al [5] found a deletion at the RB locus in a metastasis from the nasal tumor that was not present in normal tissues, in the case studied by Saw et al [6], there was no cytogenetic alteration at band 13q14. Both of our cases showed diffuse nuclear immunoreactivity for RB protein, indicating that inactivation of the RB gene is not likely to have occurred.

Concerning the pathogenesis, epidemiologic studies on large cohorts of patients with RB have shown that radiotherapy may contribute to the significantly increased risk for second tumors, including carcinomas of the nasal cavities [2,3]. Interestingly, neuroendocrine carcinoma and small cell carcinoma of the sinonasal tract have been reported as second malignancies also in adult patients treated with radiotherapy for nasopharyngeal undifferentiated carcinoma and other malignancies of the head and neck [21,22]. No difference in



**Fig. 3** Case 2, P72R (c.215 C > G) heterozygous mutation in exon 4 of TP53 gene.

terms of prognosis has been noted between postirradiated and sporadic tumors [22].

In conclusion, we present the clinicopathologic features of 2 tumors developing in children after treatment of RB, which belong to the spectrum of neuroendocrine carcinoma of the sinonasal tract. It is important to recognize the existence of these rare tumors and to differentiate them from other sinonasal neuroectodermal neoplasms, particularly Ewing sarcoma and olfactory neuroblastoma. Indeed, these malignancies have different natural histories and therapeutic regimens because patients affected by olfactory neuroblastoma have excellent outcomes with surgery and radiotherapy alone, whereas the use of specific chemotherapeutic regimens is indicated for neuroendocrine carcinoma and Ewing sarcoma.

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