Sinonasal Pathology

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Sinonasal Tract Pathology

Outline

• Sinonasal (Schneiderian) papillomas
• Glandular neoplasms
• Small round cell malignant neoplasms
Sinonasal Papillomas

Definition

- Group of benign neoplasms arising from the sinonasal (Schneiderian) mucosa and composed of squamous or columnar epithelial proliferation with associated mucous cells

Sinonasal Papillomas

Classification

- Inverted type
- Exophytic (fungiform, septal) type
- Oncocytic (cylindrical or columnar cell) type

<table>
<thead>
<tr>
<th>Sinonasal Papillomas: Clinicopathologic Features</th>
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<tr>
<td>Percentage</td>
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Sinonasal Papillomas
Clinical Features

- Typically, unilateral; bilateral papillomas, in particular the inverted subtype, may occur with reported incidence of up to 10%
- Symptoms: airway obstruction, epistaxis, an asymptomatic mass and pain
- May occur simultaneously with nasal inflammatory polyps
- Radiology - varies with extent of disease:
  - soft tissue density is seen early in the disease;
  - opacification and mucosal thickening are present with more extensive disease;
  - evidence of pressure erosion of bone may be seen

Inverted Type

Inverted Type
Intraepithelial Cysts; Mucocytes

Exophytic (Septal) Type

Exophytic (Septal) Type
Sinonasal Papilloma, Inverted Type
Differential Diagnosis

- Sinonasal inflammatory polyps
- Non-keratinizing respiratory ("transitional") carcinoma

Sinonasal Inflammatory Polyp

Sinonasal Inflammatory Polyp
SNT Polyp - Pseudolymphangiomatous Change

ERG

D2-40

Antrochoanal Polyp

Antrochoanal Polyp – vascular thrombosis and atypical stromal cells
Atypical stromal cells

Allergic Fungal Sinusitis – “Allergic Mucin”

Eosinophils and Charcot-Leyden Crystals
Sinonasal Inflammatory Polyp
High-Grade Intraepithelial Dysplasia

Sinonasal Nonkeratinizing Carcinoma
Sinonasal Nonkeratinizing Carcinoma

Sinonasal Papilloma, Septal Type
Differential Diagnosis

• Squamous papilloma

Sinonasal Papilloma, Oncocytic Type
Differential Diagnosis

• Rhinosporidiosis
• Low-grade papillary adenocarcinoma
### Sinonasal Papillomas: Clinicopathologic Features

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### Sinonasal Papillomas

**Treatment and Prognosis**

- Any sinonasal papilloma that shows moderate to severe dysplasia or has surface keratinization should prompt thorough histologic examination of all resected tissue to exclude the presence of malignancy
- No correlation between the number of recurrences and the development of carcinoma
Sinonasal Adenocarcinoma

- Heterogenous group of tumor types, including minor salivary gland origin and surface-derived

Sinonasal Glandular Neoplasms Classification

- Benign (Adenomas):
  - Minor salivary gland neoplasms
- Malignant (Adenocarcinomas):
  - Minor salivary gland neoplasms
  - Non-salivary gland, non-intestinal type
  - Intestinal type (ITACs)
**Sinonasal Adenocarcinoma**

- Represent 10-20% of all malignant sinonasal tract tumors
- Nonintestinal and Intestinal types
- Salivary gland types (adenoid cystic carcinoma >> others (acinic cell adenocarcinoma, adenocarcinoma, NOS, mucoepidermoid carcinoma, others)

**Sinonasal Adenocarcinoma, Low-Grade**

- Sinonasal Adenocarcinoma
  - Non-Intestinal Type
  - No gender predilection
  - Most often occur in 5th-7th decades of life
  - Most common in ethmoid sinus but may occur anywhere in the SNT
  - Nasal obstruction and/or epistaxis
  - No occupational or environmental exposure
Sinonasal Adenocarcinoma, Low-Grade

Sinonasal Adenocarcinoma Immunohistochemistry

- Consistently and intensely CK7 reactive
- Basal/myoepithelial markers negative
- Non-reactive for CK20, CDX2, SATB2, villin, claudins, chromogranin or synaptophysin

Sinonasal Adenocarcinoma, Low-Grade

CK7

CK20
The *ETV6-RET* gene fusion is found in *ETV6*-rearranged low-grade sinonasal adenocarcinoma without *NTRK3* involvement.

Andreasen et al. Am J Surg Pathol 2018; Published ahead press
Sinonasal Adenocarcinoma, High-Grade

Sinonasal Adenocarcinoma, Nonintestinal Type
Differential Diagnosis

- Reactive glandular proliferation
- Sinonasal hamartomas
- Sinonasal papillomas
- Intestinal-type adenocarcinomas
- Salivary gland neoplasms:
  - Adenomas (Pleomorphic; monomorphic)
  - Adenocarcinomas

Inflammatory Polyp with Mucinous Metaplasia
Sinonasal Hamartomas

- Respiratory epithelial adenomatoid (READ) hamartoma
- Seromucinous hamartoma
- Chondroosseous and respiratory epithelial (CORE) hamartoma
- Nasal chondromesenchymal hamartoma
Seromucinous Hamartoma

Sinonasal Adenocarcinoma, Nonintestinal Type
Treatment and Prognosis

- Complete surgical resection
- XRT may be used for extensive disease and/or higher grade tumors
- Prognosis depends on histologic type:
  - low-grade: 70-82% 3-year survival
  - high-grade: 20% 3-year survival
Sinonasal Adenocarcinoma
Intestinal Type (ITAC)

• More common in men than women
• Most often occur in 5\textsuperscript{th}-7\textsuperscript{th} decades of life
• Most common in ethmoid sinus (40\%) > nasal cavity (inferior and middle turbinates) and maxillary sinus; may arise anywhere in sinonasal tract
• Early symptoms tend to be non-specific (stuffiness, obstruction; may be associated with epistaxis
• Due to the delay in diagnosis, tumors may reach a large size with extensive invasion at the time of presentation

Sinonasal Adenocarcinoma
Intestinal Type (ITAC)

• Advanced tumors present with pain, cranial nerve deficits, visual disturbances and exophthalmos
• May be associated with occupational or environmental exposures:
  – hardwood dust, leather and softwood;
• Sporadic ITACs unassociated with occupational exposure occur; tend to affect women > men; most tumors involve the maxillary antrum

Classification Sinonasal Tract Intestinal-type Adenocarcinoma (ITACs)

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<td>Solid-type</td>
<td>PTCC-III 20%</td>
<td>36%</td>
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<td>Alveolar goblet uncommon 48%</td>
<td></td>
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Colonic Type

Papillary Type
Solid Type

Mucinous Type

Signet Ring Cells
Sinonasal ITACs
Immunohistochemistry

- Diffusely positive pancytokeratins, EMA, B72.3, Ber-EP4
- CEA staining is variable
- CK20 positivity (73% to 86%) and variably CK7 reactivity (43% to 93% of cases);
- CDX-2, SATB2 positive
- Expression of villin and claudins also present
- Neoplastic cells may express a variety of hormone peptides, including serotonin, cholecystokinin, gastrin, somatostatin and leu-enkephalin
- Chromogranin and synaptophysin positive cells can be identified

Sinonasal ITACs
Immunohistochemistry

CDX2  CK20  Villin

Sinonasal ITACs
Genomic Alterations

- KRAS mutation: 6-40%
- TP53 mutation: 40%
- BRAF: 10%
- EGFR alteration: uncommon
- PI6 abnormalities: promoter methylation or LOH of 8p12
- Microsatellite stable
Sinonasal ITACs
Differential Diagnosis

- Papillary sinusitis
- Metastatic adenocarcinoma of GIT:
  - rare occurrence to the sinonasal tract;
  - clinical history is critical in establishing a diagnosis of ITAC and in excluding a metastasis to the sinonasal tract from GIT primary neoplasm;
  - histology, histochemistry and IHC of ITACs and GIT adenocarcinomas are identical
- Non-intestinal, non-salivary gland adenocarcinoma

Sinonasal ITACs
Differential Diagnosis

- Salivary gland type adenocarcinoma
- Sinonasal renal cell-like adenocarcinoma (CAIX, PAX2; PAX8 positive)
- Nasopharyngeal papillary low-grade adenocarcinoma

Papillary Sinusitis
Classification Sinonasal Tract Intestinal-type Adenocarcinoma (ITACs)

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SNT Undifferentiated Malignant Neoplasms

- Squamous Cell Carcinoma
- Sinonasal Undifferentiated Carcinoma (SNUC)
- NUT Midline Carcinoma
- SMARCB1 (INI-1)-Deficient Carcinoma
- HPV-associated carcinoma with adenoid cystic-like features (now HPV-associated multiphenotypic sinonasal carcinoma)
- Olfactory Neuroblatoma
- Mucosal Malignant Melanoma
- Neuroendocrine Carcinomas
- Malignant Lymphoma (NK/T cell Lymphoma)
- Rhabdomyosarcoma
- Ewing Sarcoma
**Sinonasal Undifferentiated Carcinoma (SNUC)**

**Definition**

- A high-grade malignant epithelial neoplasm of the nasal cavity and paranasal sinuses of uncertain histogenesis with or without neuroendocrine differentiation but without evidence of squamous or glandular differentiation (Frierson et al. AJSP 1986)

**SNUC**

**Definition**

- A highly aggressive and clinico-pathologically distinctive carcinoma of uncertain histogenesis that typically presents with locally extensive disease; it is composed of pleomorphic tumor cells with frequent necrosis, and should be differentiated from other carcinomas or olfactory neuroblastoma (WHO 2004)

**SNUC**

**Definition**

- An undifferentiated carcinoma of the sinonasal tract without glandular or squamous features and not otherwise classifiable (WHO 2017)
SNUC Clinical Findings

- Uncommon
- Male predominance (2-3:1)
- Broad age range (3rd-9th decades); median age at presentation 6th decade
- Presents as large mass involving multiple sites with extensive invasive growth
- Multiple symptoms: nasal obstruction, epistaxis, proptosis, cranial nerve palsies, visual disturbances, pain, other
- Symptoms are usually of short duration (weeks to months)

3 weeks later

3 weeks later
SNUC
Etiology

• No known etiologic agents
• Negative for Epstein-Barr virus (EBER)
• Some cases reported to develop after radiation therapy for nasopharyngeal carcinoma
• Deletion of RB gene

SNUC
Etiology

• Some associated with high risk human papillomavirus (HPV):
  – HPV (p16 immunohistochemistry and molecular analysis) identified in a limited number of cases
  – uncertain relationship between HPV and SNUC
  – “If (EBV or) HPV is detected, the diagnosis of SNUC should be questioned” (WHO 2017)
SNUC
Special Stains/Studies

- Electron Microscopy:
  - rare membrane-bound, dense core neurosecretory granules
  - poorly formed desmosomes may occasionally be found

SNUC
Recurrent IDH2 R172X mutations*

- 11 cases; found in 6 (55%)
- IDH2 R172X specific to SNUCs among head and neck carcinomas confirming distinct clinicopathologic entity

*Jo VY et al. Modern Pathology 2017;30:650-9
SNUC
Differential Diagnosis

• Other sinonasal tract (small round cell) malignancies
• Nasopharyngeal Carcinoma, Undifferentiated Type; Sinonasal lymphoepithelial-like carcinoma
• Diagnosis of exclusion

NUT Carcinoma

• Poorly-differentiated carcinoma often with squamous differentiation defined by the presence of Nuclear protein in Testis (NUT) gene (NUTM1) rearrangement
• Vastly under-recognized and under-diagnosed
• Diagnosis should be considered in any non-smoking patient with poorly-differentiated squamous cell carcinoma
Definition

- Rare carcinoma characterized by:
  - basaloid and rhabdoid cells
  - loss of IHC expression of SMARCB1 (INI1)
  - SMARCB1 deletions by FISH
  - do not harbor HPV or NUT-1 alterations
  - Apparent aggressive clinical course
    including increased incidence of tumor-related mortality

SMARCB1 (INI-1) Deficient Carcinoma

Rhabdoid &/or Plasmacytoid Cells

Malignant Melanoma (MM)

- MMM neural crest-derived neoplasms originating from melanocytes and demonstrating melanocytic differentiation
- 15-20% of MM occur in the H&N:
  - > 80% cutaneous
  - orbital > oral > other upper aerodigestive tract

Sinonasal Mucosal Malignant Melanoma

Clinical Findings

- Represent approx. 1% of all MM and 2-8% of SNT malignancies
- More common in men; 6th-8th decades
- Sites: Nasal cavity > paranasal sinuses:
  - septum, lateral nasal wall
  - maxillary > ethmoid, frontal, sphenoid
- Nasal obstruction, epistaxis, pain
- No known risk factors (? melanosis)
Epithelioid cells

Clear Cytoplasm

Plasmacytoid
Spindle cells & Epithelioid cells

Spindle cells (sarcomatoid)
Sinonasal Mucosal Malignant Melanoma Molecular Studies

• **BRAF** mutations:
  – present in 50-60% of cutaneous malignant melanoma
  – uncommon in SMMM (<20% of cases)

• **c-kit**:
  – somatic mutations of c-kit with oncogenic point mutations in less than 20% of SMMM

• **NRAS** mutations:
  – appear to be relatively more frequent than **BRAF** and **c-kit**
Sinonasal Mucosal Malignant Melanoma
Differential Diagnosis

- Other undifferentiated malignancies
- **Rule Out**: metastasis from a cutaneous MM

Sinonasal Mucosal Malignant Melanoma
Treatment and Prognosis

- Surgery plus adjuvant therapy
- Poor prognosis:
  - 5-year: <30%; median 2-yr survival
  - local recurrence: 40-85%
  - distant metastasis: 30-70%
  - regional (nodal) metastasis: 10-30%
- Histopathologic determination of anatomic level of invasion (Clark level) and thickness of tumor (Breslow thickness) utilized for cutaneous malignant melanomas and are not applicable to MMM

Sinonasal Tract Malignant Lymphomas

- Full spectrum of NHL occur in SNT
- Nasal cavity → angiocentric NK/T cell
- Paranasal sinuses → B-cell lymphoma:
  - large cell
  - MALT-type
  - other
Extranodal NK/T Cell Lymphoma
Clinical Findings

- Distinct clinicopathologic entity associated with EBV
- May be localized, multifocal or systemic
- Asians >>> Western populations
- M > F; all ages but most common in 5th decade
- Sites:
  - SNT
  - extranasal: skin/subcutaneous, GIT, LN, CNS
- Symptoms:
  - midline destructive process: mucosal ulcers, obstruction, epistaxis; palatal and orbital involvement
  - discrete mass
Extranodal NK/T Cell Lymphoma
Immunohistochemistry

- CD3 + (cytoplasmic)
- CD5 +
- CD45 (LCA)
- CD56 +
- Cytotoxic molecules (TIA-1, granzyme, perforin)
- CD30 + in some cases
- EBER +
Extranodal NK/T Cell Lymphoma

Differential Diagnosis

• Infectious diseases
• Vasculitic diseases (Granulomatosis with polyangiitis [GPA] – formerly Wegener granulomatosis)
• Neoplasms:
  – Carcinoma
  – Melanoma
  – Sarcoma
GPA Histologic Features

- Majority of GPA patients do not exhibit classic histologic findings at time of initial presentation

GPA Histologic Features*

- Vasculitis, necrosis, granulomatous inflammation:
  - 16% of cases
- Vasculitis, granulomatous inflammation:
  - 21% of cases
- Vasculitis and necrosis:
  - 23% of cases

*Devaney et al. AJSP 1990;14:555-64

GPA Laboratory Findings

- Elevated Anti-Neutrophil Cytoplasmic Autoantibodies (ANCA):
  - c-ANCA (specific); n-ANCA (non-specific)
  - 50-67% positivity in LGPA
  - 60-100% positivity in GGPA
  - negative ANCA does not exclude diagnosis
  - correlation of c-ANCA with disease activity
GPA Laboratory Findings

• Proteinase 3 (PR-3):
  – Major target antigen of ANCA with a c-ANCA staining pattern in GPA
  – Detection of ANCA directed against proteinase 3 (PR3-ANCA) is highly specific for GPA

GPA Diagnosis of Exclusion

• Histologic findings often meager “negative” or descriptive dx may be of little/no help in excluding dx
• If histologic features do not support diagnosis of GPA but clinical index of suspicion for GPA is high, additional biopsies may be indicated
• Steroid treated prior to biopsy can suppress histologic features and make histologic diagnosis even more difficult and problematic
• Laboratory correlation
Rhabdomyosarcoma (RMS)
Definition

• Malignant mesenchymal neoplasm of skeletal muscle cells (rhabdomyoblasts)
Head & Neck RMS
General Considerations

• Most common sarcoma of the H&N:
  – All ages: represents up to 50% of H&N sarcomas;
  – Pediatric RMS: represents up to 75% of H&N sarcomas
• Sites:
  – orbit > nasopharynx > ME/mastoid > SNT
• Symptoms dependent on site of occurrence

Sinonasal Tract RMS
Clinical Findings

• M=F; 1st and 2nd decades of life but occurs in adults
• Symptoms: nasal obstruction, rhinorrhea, epistaxis, sinusitis, pain, otalgia, headache, proptosis, visual disturbances, cranial nerve deficits
• Polypoid appearing mass that clinically may simulate the appearance of a nasal polyp (25% of RMS in the SNT are botryoid type)
• No known etiologic factors
Rhabdomyosarcoma (RMS)  
Histologic Types

- Embryonal:  
  - most common type (80-85%)  
  - Botryoid type  
  - spindle cell type  
- Alveolar:  
  - 10-15%  
  - more frequent in adult population  
- Pleomorphic RMS
RMS Special Stains

- Histochemistry:
  - diastase-sensitive, PAS-positive (glycogen)
- IHC:
  - Myogenic markers: desmin, HHF35, myogenin (myf-4), myoglobin
  - Vimentin
RMS
Genetic Abnormalities

• Alveolar RMS:
  – t(2;13)(q36;q14) translocation – 60% of cases:
    • results in a PAX3-FOXO1A fusion gene on chromosome 13 and a FOXO1A-PAX3 fusion gene on chromosome 2
    • PAX3-FOXO1A fusion appears to be more sensitive and specific than FOXO1A-PAX3 in detecting RMS

• Alveolar RMS:
  – t(1;13)(p36;q14) translocation – 20% of cases; juxtaposes PAX7 gene on 1p36 with FOXO1A gene on 13q14;
  – approximately 80% have PAX3-FOXO1A fusion or PAX7-FOXO1A fusion
  – approximately 20% lack either of these fusions
Biphenotypic Sinonasal Sarcoma

- Low-grade spindle cell sarcoma with distinctive histological, IHC and molecular features:
  - Recurrent \textit{PAX3-MAML3} gene fusion; subset harbor \textit{PAX3-FOX01} & \textit{PAX3-NCOAI} same as alveolar RMS
- Low-grade sinonasal sarcoma with neural and myogenic features
- Intimate association with epithelial proliferation (glands invaginating from surface)

SNT Pathology
Conclusions

- Discussed histologic spectrum and differential diagnosis of:
  - Sinonasal papillomas
  - Sinonasal Adenocarcinomas:
    - Non-intestinal, non-salivary gland
    - ITACs

SNT Pathology
Conclusions

- SCC is the most common malignant neoplasm
- SNT is host to neoplasms of varied histogenesis
- Many of these “other” neoplasms are undifferentiated and share overlapping clinical and histopathologic features
- Differentiation may require IHC and molecular analysis
- Therapy and prognosis may vary per tumor type
Sinonasal Papillomas
Treatment and Prognosis

• Complete surgical excision, including adjacent uninvolved mucosa
• Adequate surgery includes a lateral rhinotomy or medial maxillectomy with en bloc excision
• All histologic types will recur if incompletely resected:
  – recurrence probably represents persistence of disease rather than multicentricity of the neoplasm
• In general, prognosis is good following complete surgical excision; however, if left unchecked, these neoplasms have the capability of continued growth with extension along the mucosal surface with destruction of bone and invasion of vital structures
Sinonasal Papillomas  
Treatment and Prognosis  

- Adjuvant therapy (chemo-and radiotherapy) has not been shown to be of benefit in sinonasal papilloma  
- Complications include recurrence and malignant transformation:  
  - majority of the malignancies are squamous cell carcinomas (keratinizing and non-keratinizing), less frequently, other carcinomas may occur including verrucous carcinoma, mucoepidermoid carcinoma, small cell carcinoma, adenocarcinoma and sinonasal undifferentiated carcinoma  
  - may occur synchronously or metachronously

Sinonasal Papillomas  
Treatment and Prognosis  

- No reliable histologic features that predict which papillomas are likely to become malignant:  
  - increased cellularity, pleomorphism, and increased mitotic activity do not necessarily become malignant  
  - presence of moderate to severe epithelial dysplasia is a potential indicator of malignant transformation  
  - surface keratinization and dyskeratosis anecdotally been considered as possible predictors of malignant transformation

Sinonasal Papillomas  
Treatment and Prognosis  

- Treatment for malignant transformation of a sinonasal papilloma includes surgery and radiotherapy  
- Prognosis for patients with malignant transformation varies:  
  - In some patients the carcinomas are only locally invasive with favorable prognosis following treatment;  
  - In other patients there may be extensive invasion with involvement of vital structures and/or metastatic disease; these patients generally have a poor clinical outcome irrespective of therapeutic intervention
Sinonasal Adenocarcinoma, Nonintestinal Type
Pathologic Features

• Low-grade:
  – circumscribed but unencapsulated
  – glandular and papillary growth
  – uniform appearing glands or acini with back-to-back growth devoid of intervening stroma; single layer of nonciliated cuboidal to columnar cells with pleomorphism and mitotic activity; no atypical mitoses or necrosis

• High-grade:
  – invasive; predominantly solid but may have glandular and papillary growth
  – back-to-back growth devoid of intervening stroma; single layer of nonciliated cuboidal to columnar cells with moderate to marked pleomorphism and increased mitotic activity, including atypical mitoses, and necrosis
**Sinonasal ITACs**  
*Treatment and Prognosis*  
- Complete surgical excision, generally via a lateral rhinotomy; depending on the extent and histology of the neoplasm surgery varies from local excision to more radical procedures (maxillectomy, ethmoidectomy and additional exenterations)  
- Radiotherapy may be utilized for extensive disease or for higher grade neoplasms  
- All considered potentially aggressive, lethal tumors  
- Metastasis to cervical lymph nodes and spread to distant sites are infrequent occurring in about 10% and 20%, respectively

**SNUC**  
*Special Stains*  
- Histochemistry: noncontributory  
- IHC: consistently immunoreactive with epithelial markers:  
  - pancytokeratin (AE1/AE3) simple keratins, (CK7, CK8, CK18) +; CK5/6 negative  
  - p63 variably positive; p40 typically negative  
  - INI-1 retained  
  - NSE, SYN, CHR may be positive  
  - S100 protein, CD57 rarely +  
  - vimentin, NUT, EBER, myogenic, hematolymphoid, melanocytic cell markers absent

**SNUC**  
*Treatment and Prognosis*  
- Multimodality therapy considered best treatment approach to provide best chance for survival and includes radical surgery and postoperative chemoradiotherapy  
- Highly aggressive neoplasm with poor survival  
  - median overall survival of 22.1 months  
  - 3-, 5- & 10-year survival rates of 44% , 35% and 31%, respectively
Extranodal NK/T Cell Lymphoma

- Cytologic spectrum is broad:
  - mixture of neoplastic and nonneoplastic cells
  - detection of EBV invaluable in early disease
- Necrosis is virtually a “constant feature”:
  - zonal (geographic) pattern
- Angiocentricity:
  - preferential concentration of tumor cells around and within bv’s with infiltration & destruction
  - not required for the diagnosis

Extranodal NK/T Cell Lymphomas

Treatment and Prognosis

- Staging is a requirement following diagnosis
- Majority are localized at presentation (Ann Arbor Stage IIE) treated by radiation alone or chemoradiation
- In some patients, surgical resection may be needed for symptomatic relief (e.g. airway obstruction)
- Stage I/II: 70-80%; Stage III/IV: up to 50%
- Amount of EBV DNA in plasma represents surrogate biomarker of lymphoma with diagnostic & prognostic significance
Extranodal NK/T Cell Lymphoma

Treatment and Prognosis

- Prognosis:
  - 25% → systemic disease → short survival
  - extranasal lesions → highly aggressive, short survival
  - death due to progressive disease
  - PD1 blockade with pembrolizumab effective in relapsed/refractory disease (Blood 2017;129:2437-42)

RMS

Treatment and Prognosis

- Multimodality therapy (surgery, radiotherapy, chemotherapy)
- Intergroup Rhabdomyosarcoma Study (IRS):
  - orbit: 92% 5-year survival
  - H&N, non-prostate bladder: 80% 5-year survival
  - parameningeal, bladder, prostate, extremities: 70% 5-year survival
  - poorest prognosis seen in association with RMS of retroperitoneum, biliary tract and peritoneum