APPENDIX A
RHABDOMYOSARCOMA

A.0 INTRODUCTION

Rhabdomyosarcoma (from Greek, rhabdo, meaning rod shape, and myo, meaning muscle) is the most common soft tissue sarcoma in children. This disease was first described in 1854 by Weber⁶, but it was not until 1946 that Stout provided a clear histological definition when he recognised the distinct morphology of rhabdomyoblasts. Stout described rhabdomyoblasts as appearing in round, strap, racquet and spider forms⁶.

Rhabdomyosarcoma is a highly malignant tumor of childhood, which spreads by local extension, and lymphatic and haematogenous dissemination⁸. According to Rubin, it is derived from primitive mesenchyme that retained the capacity for skeletal muscle differentiation⁶. Rhabdomyosarcoma of the head and neck is primarily a disease of the first decade of life, and it is the most common soft tissue sarcoma observed in childhood. Of rhabdomyosarcoma cases, 90% are diagnosed in individuals younger than 25 years, and within this group, 60-70% are younger than 10 years⁶.

This disease does not show a propensity for any particular geographic location or ethnic group. Asians have a slightly lower prevalence than blacks or whites do, and the male – to-female ratio is approximately 1.5: 1⁶. The head and neck are the most frequent sites of origin for rhabdomyosarcoma (35-40%), followed by the genitourinary tract, extremities, trunk, retroperitoneum, and other less common regions (e.g., intrathoracic, GI tract). Parameningeal rhabdomyosarcomas are tumours that arise from sites adjacent to the meninges, including the nasopharynx and nasal cavity, middle ear and mastoid, paranasal sinuses, and pterygopalatine and infratemporal fossa⁷. Rhabdomyosarcoma is a curable disease, with a 5 year survival rate of nearly 70%⁶.
A.1 CAUSES OF RHABDOMYOSARCOMA

The cause of rhabdomyosarcoma is unclear. Several genetic syndromes and environmental factors are associated with increased prevalence of rhabdomyosarcoma\textsuperscript{42}.

# Genetic syndromes include the following:
1. Neurofibromatosis
2. Li-Fraumeni syndrome (germline mutation of the tumour suppressor gene TP53)
3. Rubinstein-Taybi syndrome
4. Gorlin basal cell nervous syndrome
5. Beckwith-Wiedemann syndrome

# A higher prevalence of congenital anomalies in the following organ systems exists in patients who later develop rhabdomyosarcoma.
1. Genitourinary tract
2. Central nervous system
3. Gastrointestinal tract
4. Cardiovascular system

# Environmental factors appear to have an influence on the development of rhabdomyosarcoma, as follows:
1. Parental use of marijuana and cocaine
2. Intrauterine exposure to radiation
3. Prior exposure to alkylating agents

A.2 SYMPTOMS

Rhabdomyosarcoma generally presents as a painless large mass detected by the parent or examining physician\textsuperscript{43}.
A.3 HISTOLOGY

Traditionally, rhabdomyosarcoma was classified according to the system of Horn and Enterline as: embryonal, alveolar, botryoid, embryonal and pleomorphic\(^4^4\). The pie chart below shows the percentage distribution of the various histologies.

![Pie chart showing classification of rhabdomyosarcoma according to histology](chart.png)

A.3.1 EMBRYONAL

Embryonal rhabdomyosarcoma is the most common subtype observed in children, accounting for 60-70% of all rhabdomyosarcoma cases in this age group\(^6^4^4\). As stated these tumors can occur at any site, but they are most commonly observed either in the genitourinary region or the head and neck region. Histologically, they have high cytologic variability, representing several stages of skeletal muscle morphogenesis. They may range from highly differentiated neoplasms containing rhabdomyoblasts with large eosinophilic cytoplasm and cross striations to that of poorly differentiated tumor cells.
Embryonal rhabdomyosarcoma also has unique molecular characteristics; showing a loss of specific genomic material from the short arm of chromosome 11. This consistent loss of the material from the 11p15 region may suggest the presence of a tumor suppressor gene, although the actual gene responsible for embryonal rhabdomyosarcoma is not yet known.

Figure A.1. Embryonal rhabdomyosarcoma is evidenced by variable cell population consisting of small round tumor cells with hyperchromatic nuclei and larger polygonal-shaped tumor cells with abundant eosinophilic cytoplasm, often containing diagnostic cross striations (arrow). (Image provided by Scott Kilpatrick, MD, Department of Pathology, University of North Carolina Hospitals).

A.3.2 ALVEOLAR

The alveolar subtype makes up about 20% of rhabdomyosarcoma cases. It is more frequently observed in adolescents and in patients where the primary site involves the
extremities, the trunk, and the perianal/perirectum region. Microscopically, these tumors have the appearance of club-shaped tumor cells arranged in clumps and outlined by fibrous septa. In the centre, the clusters are arranged loosely, and thus they appear as an alveolar pattern. This tumor is the second most commonly occurring type of rhabdomyosarcoma and is the most frequently found in the extremities. Unlike embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma commonly demonstrates gene amplification, and its DNA content is typically tetraploid\textsuperscript{6}.

**Picture Type: Photo**

Figure A.2. Alveolar rhabdomyosarcoma is evidenced by uniform cell population consisting of cells with high nuclear-to-cytoplasmic ratios. The cells are arranged in variably size nests separated by fibrous tissue septa. In places, the cells appear loosely dispersed mimicking a pulmonary alveolar pattern. (Image provided by Scott Kilpatrick, MD, Department of Pathology, University of North Carolina Hospitals).
A.3.3 BOTRYOID

Botryoid type, a subset of embryonal rhabdomyosarcoma, accounts for 10% of all cases of rhabdomyosarcoma. Characteristically, this subtype arises under the mucosal surfaces of body orifices. It is distinguished by the formation of polypoid grapelike tumor masses, and it histologically demonstrates malignant cells in an abundant myxoid stroma.

A.3.4 PLEOMORPHIC

Pleomorphic rhabdomyosarcoma is the least common of all subtypes. It most often occurs in patients aged 30-50 years. It is rarely observed in children. Its cells are irregularly arranged and vary in size, thus its pleomorphic distinction. Cross striations are virtually nonexistent.

A.4 PROGNOSTIC FACTORS

Multiple clinical and biological factors have been shown to influence the prognosis of a child with rhabdomyosarcoma. These include site of tumor origin, tumor size, nodal involvement, histology and cellular DNA content. Staging classifications based on these factors allows the clinician to determine an overall prognosis for each patient.

Clinically, the site of origin for rhabdomyosarcoma influences patient outcome. For example, the orbit and non-parameningeal head and neck sites carry a more favourable prognosis, while parameningeal rhabdomyosarcomas have a propensity for central nervous system extension and have historically been associated with a poorer prognosis. Individuals with a tumor size less than 5 cm have an improved prognosis when compared with those with larger tumors. Children with regional nodal involvement do less well than those without nodal disease. Children with metastatic disease have the poorest prognosis and this is further altered by the histology of the disease. For patients who are younger than 10 years and have metastatic disease and embryonal histology, the
5-year survival rate is 60%\textsuperscript{6}. This percentage is lower if the histology is alveolar and the patient is older than 10 years\textsuperscript{6}.

Another clinical factor affecting prognosis is the extent of disease following initial surgical resection. Biological factors have an influence on the prognosis. The literature often mentions that the alveolar rhabdomyosarcoma carries a worse prognosis\textsuperscript{6,44}. When comparing the alveolar subtype to the embryonal type of rhabdomyosarcoma, alveolar is more common in patients with less favourable clinical features (e.g. older age, extremities involvement, distant metastasis)