AMORE (Ablative surgery, MOulage technique brachytherapy and REconstruction) for childhood head and neck rhabdomyosarcoma
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General introduction
1. Rhabdomyosarcoma with an emphasis on the head and neck region

1.1 Epidemiology

Rhabdomyosarcoma (RMS) is one of the embryonal tumors of childhood and is categorized into the group of soft-tissue sarcomas. In the Netherlands, leukemias and lymphomas account for 40% of childhood malignancies. The remaining 60% constitutes the group of the so-called 'solid tumors' of childhood. In this group, tumors of the central nervous system are the most common, followed by a group of tumors with a more or less comparable incidence: soft-tissue sarcomas, nephroblastoma (or Wilms' tumor), neuroblastoma, retinoblastoma and osteosarcoma. Thus, 60-70% of all pediatric malignancies are leukaemia, lymphoma and brain tumors. Soft-tissue sarcomas comprise some 6-8% of all malignancies in childhood. RMS is the most frequent soft-tissue sarcoma in children, accounting for 50-60% of childhood soft-tissue sarcomas, which is 4-5% of all childhood malignancies. In the year 2000, RMS constituted 4.4% of all 412 new cases of cancer in childhood in the Netherlands. The annual incidence of RMS is four to eight per million children in the USA, accounting for 250-350 new cases. In the United Kingdom, 60 children are diagnosed yearly. In the Netherlands, a mean incidence of 18 new RMS cases per year is reported from 1989 through 2000. In general, RMS is slightly more common in boys than in girls. A mean of 62% boys can be calculated from the reports of the large study groups. However, this percentage can vary with site. Caucasian children are more often affected than children of other races. RMS is predominantly a disease of young children. In general, the median age at diagnosis is 6 years and some 70% of the patients is <10 years of age. The group with the highest incidence consists of children 1-4 years of age. Four to 11% of the children are <1 year of age and RMS is rare in newborn. Some authors describe a bimodal age distribution with an early peak between 2 and 5 years and a second one between 12-18 years. This second peak appears to be closely related to site of occurrence (the extremities) and alveolar histology. In the head and neck region, 77% of the patients are younger than 12 years. Thus, RMS of the head and neck is primarily a disease of the first decade of life. RMS can emerge anywhere in the body, but the head and neck region (including the orbit) is the most common site of presentation, making up for 38% of the total number of RMS cases. The other sites include genitourinary sites (20-26%), divided into bladder, prostate and non-bladder, non-prostate (paratesticular, vulvar, vaginal or uterine), extremities (17-20%) and trunk wall and retroperitoneum, each accounting for 7-8%. RMS is the second most common malignant head and neck tumor in childhood (after malignant lymphoma), representing 8-28% of pediatric head and neck malignancies (Table 1). Within the
Table 1. Malignant tumors of the head and neck region in childhood

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Percentage</th>
<th>Soft-tissue sarcoma</th>
<th>Neuroblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaffe, 1973</td>
<td>176</td>
<td>54.5</td>
<td>11.2 RMS</td>
<td>5</td>
</tr>
<tr>
<td>Cunningham et al., 1987</td>
<td>241</td>
<td>35 HL</td>
<td>13 RMS</td>
<td>12.4 STS</td>
</tr>
<tr>
<td>Rapidis et al., 1988</td>
<td>308</td>
<td>26.7 HL</td>
<td>22.3 RMS</td>
<td>5.8</td>
</tr>
<tr>
<td>Robinson et al., 1988</td>
<td>144</td>
<td>37.5</td>
<td>7.3 STS</td>
<td>9.7</td>
</tr>
<tr>
<td>Schwaab et al., 1989</td>
<td>380</td>
<td>17 NHL</td>
<td>28 RMS</td>
<td>7</td>
</tr>
<tr>
<td>MacArthur et al., 1992</td>
<td>40</td>
<td>18 RMS</td>
<td>8 STS</td>
<td>4</td>
</tr>
<tr>
<td>Albright et al., 2002</td>
<td>3050</td>
<td>17 HL</td>
<td>7.8 RMS</td>
<td>1.6</td>
</tr>
</tbody>
</table>

HL, Hodgkin’s Lymphoma; NHL, Non-Hodgkin’s Lymphoma; RMS, rhabdomyosarcoma; STS, soft-tissue sarcoma other than RMS; *including Langerhans' cell histiocytosis (30%); § including ‘undifferentiated carcinoma of nasopharyngeal type’ (28%); ‡ including retinoblastoma (16%) and skeletal sarcomas (2%)


Head and neck region, a division into three subsites is made, based on prognosis: parameningeal, non-parameningeal and orbit (Table 2; see paragraph 1.6). RMS was first described in the head and neck region (the tongue) by Weber in 1854. Important historical case reports of RMS at other head and neck sites include those of Wollensberger, 1894 (oesophagus), Söderberg, 1933 and Karatay, 1949 (middle ear) and Glick, 1944 (larynx). The first large series was reported by Rakov in 1937. A series of 15 cases in head and neck region was described by Stobbe and Dargeon in 1950. The most common sites of presentation of non-orbital head and neck (HN) RMS in decreasing order of frequency are: nose and nasopharynx, paranasal sinuses, middle ear and mastoid, soft tissues of the neck, parapharyngeal space, infratemporal fossa and pterygopalatine fossa, parotid region, cheek, face, oropharynx, and oral cavity. Rare sites include the floor of the mouth, larynx, mandible and intracranial.

1.2 Histology
RMS is one of the ‘small blue round cell tumors’ of childhood. These tumors also include neuroblastoma, Ewing’s sarcoma, primitive neuroectodermal tumors and lymphoma. In many ways the histology of RMS resembles stages of myogenesis in the developing embryo (in week 7-10 of fetal life). Depending on the degree of differentiation, tumor cells can vary from a
primitive round cell through a spindle-cell to a multinucleated muscle fiber with the characteristic transverse and longitudinal structures. Therefore, it is postulated that RMS is derived from primitive mesenchyme cells, exhibiting a profound tendency towards myogenesis (see paragraph 1.3).

Histological diagnosis of RMS is based on the identification of specific features of the skeletal muscle lineage.\(^{34}\) RMS is further divided into different subtypes. The traditionally recognized classification system of Horn and Enterline (1958) describes four main histological subtypes based on morphology: embryonal, botryoid, alveolar and pleomorphic RMS.\(^{35}\) Botryoid RMS is regarded to be a subtype of embryonal RMS. In 1992, Cavazzana and co-workers recognized another subtype of embryonal RMS, the spindle-cell type.\(^{36}\)

Table 2. Prognostic subsites of head and neck rhabdomyosarcoma

<table>
<thead>
<tr>
<th>Orbit (25%)</th>
<th>Non-parameningeal (25%)</th>
<th>Parameningeal (50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>orbital</td>
<td>oral cavity</td>
<td>nasal cavity</td>
</tr>
<tr>
<td>eyelid</td>
<td>oropharynx</td>
<td>nasopharynx</td>
</tr>
<tr>
<td></td>
<td>hypopharynx</td>
<td>paranasal sinuses</td>
</tr>
<tr>
<td></td>
<td>larynx</td>
<td>middle ear/ mastoid</td>
</tr>
<tr>
<td></td>
<td>parotid</td>
<td>infratemporal fossa</td>
</tr>
<tr>
<td></td>
<td>cheek</td>
<td>parapharyngeal space</td>
</tr>
<tr>
<td></td>
<td>masseter muscle</td>
<td>pterygopalatine fossa</td>
</tr>
<tr>
<td></td>
<td>scalp</td>
<td>orbit with intracranial extension</td>
</tr>
<tr>
<td></td>
<td>thyroid and parathyroid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>soft tissues of the neck</td>
<td></td>
</tr>
</tbody>
</table>

(%) percentage of occurrence
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**Embryonal rhabdomyosarcoma, not otherwise specified**

Embryonal RMS was described as early as in 1894 by Berard and was first reported in the head and neck region by Stobbe and Dargeon. Histologically, this tumor consists of zones of dense and loose cellularity with (in the latter) a myxoid background, consisting of mucopolysaccharides (fig. 1). The tumor cells can exhibit all phases of myogenesis from undifferentiated mesenchymal cells to myoblasts, multinucleated myotubes and fully differentiated cross-striated muscle tumor cells. The more differentiated the tumor cells, the more obvious is the diagnosis. Frequently, however, the tumor consists of poorly differentiated cells. As a rule, the cells have nuclei that are smaller than those of an alveolar RMS and have lighter chromatine pattern. Highly characteristic are the ribbon- or strap-shaped cells with elongated nuclei. Also, foci of immature cartilage can be present. Embryonal RMS is more common in the younger age group and in the head and neck region and is less frequently encountered in the extremities.

**Figure 1.** Embryonal rhabdomyosarcoma. Hematoxylin-Eosin staining. Myxoid background in which loosely textured small cells and primitive spindle-cells with an eccentrically placed nucleus and unipolar cytoplasmic extensions, varying in size. (Courtesy: Dr. J. Bras, Dept. of Pathology, Academic Medical Center)

**Embryonal rhabdomyosarcoma, botryoid subtype**

The botryoid subtype was first described by Guersant and arises in the submucosa of a hollow space, e.g. nasopharynx, maxillary sinus, bladder, bile duct or vagina. The tumor abuts the epithelial surface and protrudes into the lumen. The gross configuration is usually grape-like and hence it is termed botryoid (Botryos is the Greek word for grape). The cellular composition beneath the epithelial covering of the polypoidal masses is essentially embryonal in pattern. The prerequisite for diagnosis is a dense subepithelial condensation of tumor cells. This condensation, which is several cells thick, is called the ‘cambium layer’ (fig. 2). The appearance of the tumor cells varies from small and primitive- (showing little myogenesis) to larger cells, with more definitive myogenesis present. When the cambium layer is absent, even in a grape-like tumor, the tumor is diagnosed as embryonal RMS. The exophytic growth is predominantly directed towards the path of least resistance, i.e. the lumen. Therefore, botryoid RMS is less invasive and carries a more favourable prognosis (vide infra).
Embryonal rhabdomyosarcoma, spindle-cell type

Spindle-cell RMS is recognized as a subtype of embryonal RMS consisting of more differentiated, elongated spindle-cells in a ‘storiform’ pattern (consisting of interdigitating fascicles) with abundant collagen between tumor cells (collagen-rich subtype), or in bundles with low collagen content (collagen-poor- or leiomyomatous subtype)\(^5\)\(^6\) (fig. 3). The latter resembles smooth muscle tumors. Spindle-cell RMS is frequently encountered at paratesticular sites.

Alveolar rhabdomyosarcoma

The alveolar subtype was initially described by Riopelle and Theriault.\(^6\)\(^1\) Alveolar RMS is composed of ill-defined aggregates of poorly differentiated round cells. These aggregates are separated by collagenous septa and frequently show central loss of cohesion with preservation of the peripheral cells. The peripheral cells adhere in a single layer to the collagenous septa, resulting in ‘alveolar’ spaces (resembling pulmonary alveoli) (fig. 4).\(^5\)\(^4\) The cells have oval or round nuclei which are larger than those of embryonal RMS and often have a thin rim of myogenic cytoplasm. Multinucleated giant cells are uncommon. The alveolar pattern can be focal, but any alveolar features are sufficient to classify the tumor as alveolar.\(^5\)\(^0\) A solid variant without the
alveolar spaces is also recognized. Alveolar RMS is generally seen in the older age group (children or young adults), but can occur at any age, and is most frequently encountered at trunk and extremity sites. The clinical behaviour of alveolar RMS is more aggressive, when compared to the other subtypes. Lymph node and distant metastases are more common and the prognosis is worse (see paragraph 1.6.2).

Figure 4. Alveolar rhabdomyosarcoma at low (A) and high (B) magnification. Hematoxylin-Eosin staining. Small cell aggregates with loss of cellular cohesion, resulting in an alveolar pattern. High magnification shows delicate fibrous septa, lined by a single row of undifferentiated cells with a small unipolar cytoplasmatic extension. (Courtesy: Dr. J. Bras, Dept. of Pathology, Academic Medical Center)

### Pleomorphic

Pleomorphic RMS, originally described by Stout in 1946 as a pleomorphic sarcoma resembling bizarre skeletal muscle cells, is the least common type recognized, especially since the introduction of immunohistochemistry in the 1980s. Immunohistochemistry made the differentiation from other pleomorphic sarcomas, e.g. pleiomorphic leiomyosarcoma and pleomorphic malignant fibrous histiocytoma possible. Pure pleiomorphic RMS is, in contrast to embryonal and alveolar RMS, predominantly a tumor of the elderly patient. However, pleomorphic areas can also be found in untreated embryonal RMS and in embryonal and alveolar RMS after chemotherapy.

Several investigators throughout the years have modified the classic Horn and Enterline classification to optimize the definition of prognostically relevant and diagnostically consistent morphologic subtypes. These efforts have resulted in different classifications. The IRS and SIOP have proposed an international classification claiming to be reproducible and strongly predictive of clinical outcome (Table 3). The botryoid and spindle-cell variants of embryonal RMS have a superior prognosis, embryonal an intermediate- and alveolar an unfavourable prognosis.
In general, approximately 60% of the rhabdomyosarcomas are of embryonal (6% botryoid and 3% spindle cell)- and 32% of alveolar histology. In the head and neck region, some 75% are embryonal and 20% alveolar.

1.3 Etiology and molecular genetics
RMS is believed to originate from embryonic mesenchymal tissue. The exact cell type from which RMS is derived is not clear. This is either immature prospective muscular tissue (myogenic precursor cells) or indifferent mesenchymal tissue (uncommitted mesenchymal stem cells) with a potency for aberrant differentiation into muscle fiber. As most sarcomas are of a single phenotype, it is, however, likely that sarcomas arise from an abnormal event in an already committed mesenchymal cell, e.g. a myogenic satellite cell in case of RMS. Tumor cells morphologically show varying degrees of skeletal muscle differentiation, from immature round cells through rhabdomyoblast stages to fully differentiated muscle fibers (see paragraph 1.2) and RMS cells express muscle specific (structural and regulatory) proteins. Therefore, tumorigenesis is believed to originate from interrupted normal skeletal muscle development. Understanding of the myogenetic pathway, i.e. the molecular events that regulate skeletal muscle development, is a prerequisite for a further discussion of RMS tumorigenesis. Normal myogenesis, RMS tumorigenesis and presumed etiologic factors (both genetic and environmental) will be described briefly.

1.3.1 Normal myogenesis
Skeletal muscle is derived from condensations of mesoderm (somites) which form during the third week of embryogenesis. The dorsolateral part of each somite differentiates into a dermatomyotome and a myotome. Induction of somatic myogenesis requires signals form the adjacent neural tube and notochord. The products of two genes wnt-1 (from the neural tube) and shh (sonic hedgehog; from the notochord) induce downstream expression of PAX3 and PAX7 in pre-somatic mesoderm. PAX 3 and PAX 7 proteins are transcription factors, encoded by the PAX gene family. Signaling through shh and wnt is negatively regulated by the gene ptc (patched), a tumor suppressor gene. It is known from experimental studies that both PAX 3 and PAX 7 play an important role in directing the migration of myogenic precursor cells. The process of
myogenic differentiation, i.e. the commitment of the somatic cells to the myoblast lineage, is believed to be regulated by the sequential expression of the myogenic regulatory factor (MRF) proteins MyoD, Myogenin, MYF5, MYF6, and MRF4. Subsequent proliferation is regulated by a variety of growth factors, like insulin-like growth factor (IGF).

### 1.3.2 RMS tumorigenesis

In RMS tumor cells, muscle structural proteins are usually expressed but there is a block to the formation of fully developed myotubes and myofilaments. The RMS phenotype as well as the expression of regulatory proteins in RMS cells therefore suggest an interrupted normal myogenic differentiation. Thus, RMS is believed to arise from regulatory disruption of the growth and differentiation of myogenic precursor cells. The abovementioned signalling pathways may be important in tumor development. Experimental studies have revealed several chromosomal aberrations (translocations, loss of heterozygosity, loss of imprinting, genomic amplification and numerical chromosome changes) associated with RMS, presumably leading to altered expression of myogenic transcription factors and growth factors. Also, proteins controlling the cell-cycle of satellite cells (such as pRB, p53, ATR and CDKs) and their inhibitors are thought to play a role in the development of RMS.

### 1.3.3 Etiologic factors

Both constitutional and somatic genetic alterations and environmental factors are believed to contribute to the development of RMS. However, in only a minority of the cases RMS can be attributed to a defined hereditary syndrome or known environmental exposure.

**Constitutional genetic factors**

The overwhelming majority of rhabdomyosarcomas appear to be sporadic in nature. There is, however, an association of RMS with congenital (genitourinary, central nervous system) anomalies and hereditary syndromes, suggesting the presence of germline mutations in some cases. Syndromic cases have revealed several chromosomal alterations that may play a role in the pathogenesis. Over the past decades, a number of genetic lesions have been associated with human RMS. In 5% of the cases RMS is associated with syndromes. The most commonly recognized syndromes are neurofibromatosis, Beckwith-Wiedemann syndrome and Li-Fraumeni syndrome (identified from a RMS index case). Other syndromes include Waardenburg syndrome, Gorlin’s syndrome (Nevoid basal cell carcinoma syndrome), Rubinstein-Taybi syndrome and adenomatous poliposis coli syndrome. RMS can also be associated with retinoblastoma.
Somatic genetic alterations

Some 90% of the alveolar RMS cases express so-called 'fusion' genes as a result of specific chromosome translocations.\(^6^8\) The most consistent translocation, found in 80% of alveolar RMS cells, is t(2;13)(q35;q14).\(^7^5,^8^4,^8^5\) This translocation juxtaposes the 5' sequence from the PAX3 gene on chromosome 2q35 with 3' sequences from the forked-head DNA binding protein (FHKR, forkhead in rhabdomyosarcoma) gene on chromosome 13q14. Both PAX and FHKR are encoding transcription factors. It is assumed that the chimeric protein encoded by the PAX3-FKHR fusion is a more potent transcriptional activator than wild type PAX3, presumably enhancing the activation of genes downstream of PAX3 and contributing to a transformed phenotype.\(^6^8\) The variant t(1;13)(p36;q14) translocation is found in 10%, leading to the PAX7-FKHR fusion gene and a distinct phenotype.\(^8^6\) These translocations can also be used for diagnostic purposes (see paragraph 1.5.4).

In embryonal RMS, (maternal) allele loss, i.e. loss of heterozygosity (LOH), on the short arm of chromosome 11 (11p15.5) is almost uniformly identified.\(^8^7,^8^8\) However, the relevant genetic target of this loss-of-function mutation has not been identified. The 11p15 region contains a number of imprinted genes implicated in oncogenesis, such as the insulin-like growth factor 2 (IGF2) gene which stimulates tumor cell growth.\(^8^9,^9^1\) This locus can show loss of imprinting (LOI).\(^6^8,^7^0\) Imprinting is an epigenetic, gamete of origin dependent, allele inactivation process. RMS tumors have been found to demonstrate LOI, coincident with active transcription from both maternal and paternal alleles (bi-allelic expression) of the IGF2 gene.\(^9^2\) This LOI can lead to a twofold gene dosage effect and may contribute to the characteristic overexpression of IGF2 observed in RMS cell lines.\(^9^3\)

Genomic amplification of the following regions has been found: 12q13 (the locus of GLI, MDM2 and CDK4), 1q21, 2p24 (N-myc) and many more.\(^7^0\) Other genetic alterations include p53 mutations (found in 50% of RMS cases), and activating mutations in N-ras and K-ras oncogenes.\(^6^8\) Embryonal RMS tumor cells have been found to have DNA contents ranging between diploid and hyperdiploid (1.1 to 1.8 times the normal amount of DNA), primarily involving gains of chromosomes 2, 8, 11, 12, and 13, with particular high-level gain of chromosome 8 material.\(^9^4,^9^7\)

Environmental factors

Potential associations with environmental factors, such as parental use of marijuana and cocaine before conception, maternal history of stillbirths, fetal alcohol syndrome, hydantoin syndrome, lower socio-economic status, paternal smoking, ingestion of organ meats and exposure to chemicals have all been suggested.\(^9^8,^1^0^1\) However, with the exception of exposure to ionizing radiation and alkylating agents, a strong association between pediatric RMS and environmental factors is lacking.
The interaction of environmental and genetic factors in children with known genetic aberrations has to be kept in mind in treatment regimes, minimizing the risk for development of second primary malignancies.

### 1.4 Signs and symptoms

Signs and symptoms of RMS patients are depending on localization. Despite its highly malignant character (see paragraph 1.6), the initial symptoms of HNRMS are often non-specific and can mimic benign conditions, like upper respiratory tract infections and allergy. A suspected infection is the most common cause of delay in diagnosis and is stated to occur in 50% of the patients.\(^\text{102}\) The average time until a correct diagnosis is made is 2-4 months.\(^\text{41,45,102-104}\)

The signs and symptoms of HNRMS patients frequently result in a referral to the ear-nose-throat (ENT) department. The symptoms depend on the site of origin of the lesion, age and presence or absence of metastatic disease. Case series of HNRMS reporting on initial symptoms mention facial swelling, progressive nasal obstruction, airway obstruction, nasal discharge, coughing, recurrent epistaxis, serous otitis media with hearing loss, aural polyps, otalgia, otorrhoea, epiphora and proptosis.\(^\text{38,41-45,50,67,102-126}\)

Later in the course of the disease, signs of infiltration will occur: trismus, deviation of the jaws, strabismus, vision loss, hoarseness, dysphagia, paresthesia and pain. Also, cervical lymph node enlargement can be encountered.

Extension (of parameningeal HNRMS) into the foramina at the base of the skull, cavernous sinus and central nervous system can eventually give neurological manifestations. These include sensory or motor cranial nerve deficits (nn VII, VI and V are most commonly affected), meningeal symptoms, signs of raised intracranial pressure (headache, vomiting, papilledema), spinal cord or brain stem compression (muscle pareses, back pain, respiratory paralysis) and vascular compression.\(^\text{26,127-130}\)

When metastatic disease is present, symptoms related to the involved organs can be seen: pain, swelling and limp in case of bone metastases and features mimicking an acute hematologic malignancy (pancytopenia and haemorrhagic diathesis accompanying DIC) in case of bone marrow involvement.\(^\text{131,132}\) Rarely, patients present with distant metastases, without evidence of a primary tumor.\(^\text{133}\) Constitutional symptoms (anorexia, fatigue, lethargy and fever) are also described.\(^\text{102}\)
1.5 Diagnosis
A full diagnostic work-up for children with RMS includes clinical assessment, imaging, biopsy and laboratory tests.

1.5.1 Clinical assessment
Clinical assessment consists of thorough head and neck examination, including visualisation of the entire upper aerodigestive tract, all cervical nodal areas and cranial nerves. The use of rigid or fiberoptic instruments may require general anesthesia in young children. Routine ENT-examination is usually sufficient to form an impression of the site, size, extent and vascularity of the primary lesion and the involvement of regional lymph nodes. Further investigative work-up is directed to determine the exact locoregional extent of the lesion, the presence of metastases and the histology.

1.5.2 Imaging
Primary site
Imaging studies are essential in assessment of the origin, size and extent of the lesion, involvement of adjacent structures (invasiveness), bone erosion, meningeal spread, and extension into the central nervous system. These features determine the feasibility of surgery, selection of surgical approach and planning of radiation treatment. Imaging studies have to be performed before biopsy, as tissue changes after open biopsy may hamper the ability to define the local extent of the disease.

Magnetic resonance imaging (MRI) (gadolinium-enhanced) is the investigation of choice for evaluation of the primary site because of its superior soft-tissue contrast. MRI is superior to computed tomography (CT) in the assessment of delineation of the tumor, extension into surrounding soft-tissues, perineural and perivascular growth, demonstration of intracranial extension, obliteration of fat planes, assessment of vascularity and differentiation of mucosal thickening and obstructed secretions from tumor. The lack of ionizing radiation is another advantage. Due to the loose stromal network and high overall water content, the appearance of RMS is hyperintense on T2-weighted images and isointense or minimally hyperintense relative to muscle on T1-weighted images (fig. 5). Hagiwara and co-workers have reported specific MRI features of botryoid RMS. CT-images are of value in the detection of early-stage cortical bone erosion. In some cases, MRI and CT-studies are complementary. There is growing evidence that Positron Emission Tomography (PET) scanning with Fluoro-2-deoxyglucose (FDG) might be useful for diagnostic purposes, based on studies in heterogeneous populations (children with solid tumors and adults with various soft-tissue sarcomas). PET detects a high glucose uptake due to the heightened metabolic rate of malignant cells compared to normal cells. However, the elevated glucose metabolism in
Chapter 1

acute inflammation represents a common cause of false positive results of PET.\textsuperscript{149} Definitive conclusions as to its specific value in pediatric RMS cannot be made, as publications are scarce and are merely limited to case reports.\textsuperscript{150-152}

\begin{center}
\textbf{Figure 5.} Spinecho T1-weighted MR image, showing a parameningeal RMS with intracranial extension and destruction of the sphenoid bone. Note the difference with the contralateral side (arrows).
\end{center}

\textbf{Metastases}

The work-up for metastases includes the search for regional cervical node involvement (imaging studies followed by fine needle aspiration cytology when lymph nodes > 1cm are found) and distant metastasis. RMS metastasizes predominantly to the lungs, skeleton and bone marrow. Therefore, a chest CT scan, skeletal scintigraphy and bone marrow aspirate are included in the work-up. Analysis of the cerebrospinal fluid (CSF) is performed only in parameningeal disease, because RMS at this particular site carries a risk for spread to the central nervous system (CNS) (see paragraph 1.6.1).

\textbf{1.5.3 Biopsy}

Biopsy techniques include fine needle aspiration cytology (FNAC), core-needle and open (incisional or excisional) surgical biopsies. FNAC is easy to perform, quick and carries minimal risks. FNAC can rule out other diseases. However, a small sample of aspirated cells is obtained and sampling errors are possible. FNAC is reported to lead to an accurate diagnosis and subclassification in 80-90\% of the cases when immunohistochemical staining is performed on the sample (fig. 6).\textsuperscript{153,154} Core-needle biopsies are even more accurate, but not always easy to perform in the head and neck region, especially at parameningeal sites.\textsuperscript{153} The open surgical biopsy maximises the tissue available. A biopsy should certainly be performed if the initial needle biopsy is non-diagnostic. Frozen section of the specimen may be used to confirm that adequate diagnostic tissue has been sampled.
1.5.4 Diagnostic techniques

Light microscopy

The diagnosis of RMS is generally based on histopathologic morphology at a light-microscopic level (see paragraph 1.2).\textsuperscript{156} Immunohistochemistry and molecular biologic techniques are essential in the differential diagnosis. Since the introduction of immunohistochemistry, electron microscopy is hardly used anymore.

The differential diagnosis of HNRMS comprises the entire spectrum of small blue round cell tumors as Ewing family of tumors (Ewing's sarcoma, PNET), malignant lymphoma, neuroblastoma and small-cell carcinoma.\textsuperscript{58,157}

Immunohistochemistry

A fair number of monoclonal and polyclonal antibodies, amongst others against skeletal muscle- and other specific structural proteins, are reliable markers for myogenic differentiation and can contribute to the diagnosis of RMS and its differentiation from other small-cell tumors.\textsuperscript{158} For instance, RMS cells express myogenin, desmin and Myo D1 (fig. 6).\textsuperscript{159} These markers are not expressed by other small-cell tumors, that might show the following staining characteristics: Ewing/ PNET shows expression for CD99, malignant lymphoma for leucocyte common antigen (LCA or CD45) and neuroblastoma for neuroendocrine markers (synaptophysin, chromogranin and CD56) and small-cell carcinoma for polykeratin (www.immunoquery.com).

Figure 6. Rhabdomyosarcoma. Cytology, showing small cells with an eccentrically placed nucleus and unipolar cytoplasmatic extensions (A, Giemsa staining). The tumor cells express desmin (B, Desmin staining).
Molecular genetic techniques
Alveolar RMS is characterized by two specific translocations, t(2;13)(q35;q14) and t(1;13)(p36;q14) (see paragraph 1.3.3). These translocations can be detected by fluorescent in situ hybridisation (FISH). Their fusion transcripts PAX3-FKHR and PAX7-FKHR can be detected by reverse transcriptase polymerase chain reaction (RT-PCR).

1.6 Clinical behavior and prognostic factors

1.6.1 Clinical behavior
Rhabdomyosarcoma in general
RMS is a fast-growing, primitive, high-grade malignant tumor. It is locally invasive, spreads along tissue planes and metastasizes to regional lymph nodes and distant sites. Clinical behavior is related to site, histology and age (see paragraph 1.6.2). In general, ~36% of the patients present with a tumor confined to the organ or tissue of origin, ~36% has a tumor that invades neighbouring organs or tissues, ~10% has regional lymph node metastases and ~18% distant metastases at diagnosis. It is estimated that micrometastases may be present at the time of diagnosis in as many as 70-80% of the cases. This explains why, prior to the advent of effective chemotherapy, many of the patients died of disseminated disease in lungs, bone marrow and/or bones.

Head and neck rhabdomyosarcoma
In non-orbital HNRMS, the diagnosis is usually made late in the course of the disease. An interval of several months between the onset of symptoms and diagnosis is common (see paragraph 1.4). This is especially true for parameningeal disease. Locally advanced, irresectable disease at presentation is found in 81-94% of the cases and 40-50% of the tumors are > 5cm. In non-parameningeal RMS, 37-45% of the tumors is locally advanced and irresectable and 24% of the tumors is >5 cm. Parameningeal disease has the propensity for spread towards the CNS. This spread can either be via the neurovascular sheets of cranial nerves through the multiple foramina and fissures at the base of the skull or through erosion and subsequent destruction of the skull base (fig. 5). The disease can subsequently reach the leptomeninges and subarachnoidal space. Actual meningeal extension can develop in up to 35% of the patients with parameningeal HNRMS and is most frequently found in association with the middle ear/ mastoid as primary site. When this occurs, treatment is rarely successful. Therefore, it is important to identify patients at high risk for meningeal spread. The following high-risk features have been defined: skull base erosion, intracranial growth and cranial nerve palsies. These features are present in ~69% of the parameningeal cases.
With respect to lymph node metastases, the incidence ranges from 3 to 38% in the various studies of HNRMS patients. The main reasons for this wide range are probably the small populations studied in single center series, different distribution of primary sites and 'aggressiveness' with which staging was performed. Lymph node involvement in large patient series is more constant: 17-20% (parameningeal disease) and 18-20% (non-parameningeal disease). As for distant metastasis, most studies report incidences between 5-11% at diagnosis. In a recent study, a very high percentage (33% of 50 HNRMS patients) of distant metastases is reported. The incidence in parameningeal disease is somewhat higher when compared to non-parameningeal HNRMS. Metastatic sites in decreasing order of frequency are the lungs, bone and bone marrow, central nervous system and abdominal viscera.

1.6.2 Prognostic factors

From the analysis of large collaborative trials it has become clear that certain tumor and patient characteristics affect survival. The prognostic importance of tumor stage, primary site, histology and age at diagnosis is outlined below.

1.6.2.1 Stage

A number of different systems have been used for the staging of children with RMS. The most important staging systems are the IRSG Clinical Grouping (CG) and the TNM-classification. The IRSG classification, as used in the consecutive IRS trials I through III, is based on surgico-pathologic grouping. Four groups are recognized, based on the amount of tumor remaining after surgery (or biopsy only) and the degree of tumor spread at the time of diagnosis (Table 4). These four groups have been found to be highly related to outcome. The use of this system, however, could introduce confounding data, based on differences between treatment philosophies and technical qualities of surgeons and pathologists. Recent changes in the therapeutic approach and the need for comparison of outcomes between study groups led to the incorporation of the presurgical TNM staging system in trials IV and V of the IRSG. The SIOP group already used the TNM-classification of the International Union Against Cancer (UICC). This classification is based on pre-treatment evaluation of tumor extent and size, regional lymph node and distant metastasis (Table 5). Pre-treatment staging minimizes the differences inherent in post-surgical clinical grouping.

Retrospective analysis of tumor stage in relation to outcome, reveals that poorest survival was observed for patients with distant metastasis (M1). In the M0 group, tumor invasiveness (T2) and tumor size (> 5 cm) adversely affected prognosis. There is conflicting evidence concerning the prognostic significance of nodal metastases. Positive nodes adversely affected outcome in some studies, whereas no relation to outcome was found in other studies.
1.6.2.2 Site

IRS and SIOP study data demonstrate that survival is influenced by the site of origin of the tumor. A division into three prognostic sites has emerged from the analysis of SIOP data: (1) superior prognosis: vagina, paratestis and orbit (2) intermediate prognosis: non-parameningeal sites (head and neck and others), (3) poor prognosis: parameningeal sites (Table 2). The IRS group classified patients into two groups with distinct survival, (1) a ‘favorable’ group of anatomic sites consisted of orbit/eyelid, genitourinary system (other than bladder and prostate) and non-parameningeal head and neck sites; (2) an ‘unfavorable’ group including parameningeal head and neck, extremities, trunk, bladder, prostate and other sites.

1.6.2.3 Histology

The prognostic relevance of histologic subtype is not consistent. In IRS I and II, prognosis was worse for patients with alveolar histology. The third IRS trial did not confirm this difference. This could, however, be due to the more intensive treatment given for alveolar RMS. In IRS IV, the histologic subtype was again found to be of influence. In an analysis of 281 SIOP patients, histology had no influence on survival. The same was found in the CWS 81 study. In the SIOP MMT84 and CWS86 studies, however, patients with alveolar tumors fared much worse. In recent classifications, RMS histologic subtypes are still divided into groups with a different prognosis (Table 3).

1.6.2.4 Age

The influence of age on outcome also varies between different trials. In the SIOP MMT84, CWS 81- and 86 and IRS I and II studies, no influence of age on outcome was found. In a study conducted by the MSKCC, survival proved to be a decreasing function of age. The effect of age was most marked in patients with locally invasive, non-metastatic tumors. In the fourth IRS trial, patients <1 and > 10 fared worse.

1.6.2.5 Molecular biology

Alveolar RMS with the PAX7-FKHR fusion gene (see paragraph 1.3.3) has a relatively more favorable prognosis compared to the PAX3-FKHR transcript. The clinical relevance of DNA ploidy is uncertain. Molecular biology is not yet used as a prognostic factor in the allocation to treatment regimens.

1.6.2.6 Prognostic factors in HNRMS

Most studies analyzing the prognostic factors in patients with HNRMS specifically, confirm the prognostic significance of IRS clinical group, T-stage and size > 5 cm. In the largest series of 611 parameningeal patients, however, size was not a prognostic factor, neither
Table 4. Post-surgical classification used by the Intergroup Rhabdomyosarcoma Study Group (IRSG)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Localized disease, completely resected (regional nodes not involved—lymph node biopsy or dissection is required except for head and neck lesions)</td>
</tr>
<tr>
<td></td>
<td>(a) Confined to muscle or organ of origin.</td>
</tr>
<tr>
<td></td>
<td>(b) Contiguous involvement—infiltration outside the muscle or organ of origin, as through fascial planes.</td>
</tr>
<tr>
<td></td>
<td><strong>NOTATION:</strong> This includes both gross inspection and microscopic confirmation of complete resection. Any nodes that may be inadvertently taken with the specimen must be negative. If the latter should be involved microscopically, then the patient is placed in group IIb or IIc (see below).</td>
</tr>
<tr>
<td>Group II</td>
<td>Total gross resection with evidence of regional spread</td>
</tr>
<tr>
<td></td>
<td>(a) Grossly resected tumor with microscopic residual disease (surgeon believes that he or she has removed all of the tumor, but the pathologist finds tumor at the margin or resection and additional resection to achieve clean margin is not feasible).</td>
</tr>
<tr>
<td></td>
<td>No evidence of gross residual tumor. No evidence of regional node involvement. Once radiotherapy and/or chemotherapy have been started, reexploration and removal of the area of microscopic residual does not change the patient's group.</td>
</tr>
<tr>
<td></td>
<td>(b) Regional disease with involved nodes, completely resected with no microscopic residual.</td>
</tr>
<tr>
<td></td>
<td><strong>NOTATION:</strong> Complete resection with microscopic confirmation of no residual disease makes this different from groups Ila and Ilc. Additionally, in contrast to group Ila, regional nodes (which are completely resected, however) are involved, but the most distal node is histologically negative.</td>
</tr>
<tr>
<td></td>
<td>(c) Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.</td>
</tr>
<tr>
<td></td>
<td><strong>NOTATION:</strong> The presence of microscopic residual disease makes this group different from group IIb and nodal involvement makes this group different from group Ila.</td>
</tr>
<tr>
<td>Group III</td>
<td>Incomplete resection with gross residual disease</td>
</tr>
<tr>
<td></td>
<td>(a) After biopsy only.</td>
</tr>
<tr>
<td></td>
<td>(b) After gross total or major resection of the primary (&gt;50%).</td>
</tr>
<tr>
<td>Group IV</td>
<td>Distant metastatic disease present at onset (lung, liver, bones, bone marrow, brain, and distant muscle and nodes)</td>
</tr>
<tr>
<td></td>
<td><strong>NOTATION:</strong> The above excludes regional nodes and adjacent organ infiltration which places the patient in a more favorable grouping (as noted under group II). The presence of positive cytology in the cerebrospinal fluid, pleural or abdominal fluids and implants on pleural or peritoneal surfaces are regarded as indications for placing the patient in group IV.</td>
</tr>
</tbody>
</table>

was T-stage in a pooled series of 230 parameningeal cases.\textsuperscript{164} Nodal status was found to be related to outcome in some studies\textsuperscript{11,166,175}, whereas this was not found in other studies.\textsuperscript{164,165,176} Orbital, non-parameningeal and parameningeal sites are each considered to have a distinct prognosis. The outcome for orbital HNRMS is the best and that of parameningeal disease the worst, with non-parameningeal being in between (see paragraph 1.8).\textsuperscript{67,180} The neck was reported to be a prognostic unfavorable site within non-parameningeal disease in one study, but this finding could not be reproduced in a series of 164 non-parameningeal cases.\textsuperscript{166} Within parameningeal sites, the subgroup of patients at high risk for meningeal extension is reported to have a less favorable outcome.\textsuperscript{29} Bone erosion at the base of the skull is stated to be an important factor.\textsuperscript{184} The outcome for high-risk versus other parameningeal patients was, however, not significantly different in the study by Benk and co-workers.\textsuperscript{164} In a pooled analysis of parameningeal cases included in IRS studies II, III and IV, the paranasal sinus and pterygopalatine and infratemporal fossa were identified as poor prognostic subsites within parameningeal disease.\textsuperscript{29}
Table 5. SIOP classification based on pre-treatment TNM staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>size</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>a or b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>a or b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>any</td>
<td>a or b</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>any</td>
<td>a or b</td>
<td>any</td>
<td>1</td>
</tr>
</tbody>
</table>

SIOP, International Society of Pediatric Oncology (Société International D’Oncologie Pédiatrique)
T, tumor extension; T1, tumor limited to organ/tissue of origin; T2, tumor invades surrounding tissues
a, tumor < 5 cm; b, tumor > 5 cm;
N, nodal involvement (0, absent; 1, present); M, distant metastases

In several studies, age ≤ 1 and > 10 years was related to a less favorable outcome. Histopathologic subtype was not consistently found to be related to outcome, but is still believed to be an important prognostic factor.

In conclusion, the results of multivariate analyses have revealed a consistent relation of distant metastases, tumor invasiveness, size > 5 cm, post-surgical stage and site with clinical outcome. The influence of histology, age and chromosomal aberrations as single independent prognostic factors is less clear. Still, all factors, with the exception of chromosomal aberrations, are used in the risk stratification in current treatment protocols (see paragraph 1.7.2).

1.7 Treatment

1.7.1 Historical perspective
Prior to 1960, extensive surgery of the primary tumor with or without small field, low-dose radiation, was the only mode of treatment for RMS patients. This often entailed extensive surgical procedures involving the removal of important organs or tissue, resulting in the loss of form and function and, in case of head and neck lesions, considerable disfigurement. Despite these radical procedures, the tumors in patients with apparently localized disease subsequently relapsed. Approximately 5-10% survived 5 years and most children died from disseminated disease. This led to the assumption that micrometastasis was present at diagnosis and forms the basis of modern therapy. In the early 1960s, new chemotherapeutic agents (vincristine, actinomycin-D and cyclophosphamide) were shown to be effective against RMS as single agents. Soon, it became apparent that combinations of these agents were even more effective and resulted in increased response rates. With the advent of multidrug chemotherapy, cure rates increased to 25% in the early 1970s. Subsequent integration of chemotherapy, surgery and radiotherapy in multimodality treatment protocols gave a further
improvement in survival rates. To date, ±70% of the children with RMS are long-term survivors.\textsuperscript{13,204}

The relative rarity of rhabdomyosarcoma as well as its marked clinical and biologic heterogeneity (e.g. the numerous primary sites, varied extent of the disease at presentation, and multiple histiotypes) made the results of relatively small studies difficult to interpret. Multimodal therapy incorporating surgery, external beam radiation therapy and chemotherapy has been developed through large collaborative trials: the Intergroup Rhabdomyosarcoma Study Group (IRSG), International Society of Paediatric Oncology (SIOP), “Cooperative Weichteil-Sarkom-Studien” (CWS) and Italian Cooperative Study (ICS). At present, all European study groups are collaborating to form a new European Soft-tissue Study Group (ESSG) and to design a trial to start in 2004.

Carefully designed trials from the various collaborative groups have led to a dramatic improvement in outcome. This improvement has not only been achieved through the development of new multimodal treatment strategies, but also because of advances in imaging (and consequently, improved treatment planning) and supportive care.

1.7.2. Risk-based treatment allocation

In current treatment protocols, patients are stratified according to the prognostic factors that have emerged from the abovementioned trials (see paragraph 1.6.2) to provide a ‘tailored’, risk-based treatment. The factors histology, post-surgical stage (according to IRS-grouping), tumor site, nodal involvement, tumor size and patient age determine the risk-profile for each patient. According to this risk profile, the patient is allocated to a therapeutic regimen. In this way overtreatment is avoided in patients with a good prospect for cure, whereas high-risk patients receive more intensive treatment. The aim of each regimen is to achieve cure with the least morbidity. We have attempted to summarize the guidelines for treatment of HNRMS, derived from all major study groups (fig. 7). Details of the different treatment modalities for both primary and salvage treatment of non-metastatic RMS, with an emphasis on HNRMS, are outlined below.

1.7.3 Primary treatment

1.7.3.1 Chemotherapy

Agents widely used in the treatment of RMS include (1) alkylating agents: ifosphamide (I), cyclophosphamide (C), cisplatin, carboplatin, melphalan; (2) antibiotics: actinomycin-D (A), adriamycin or doxorubicin (Adr), epirubicin (epiadriamycin); (3) plant alkaloids: vincristine (V), etoposide or VP16(E) and (4) antimetabolites: methotrexate. All cooperative study groups have been using combinations of agents in their subsequent trials. The number, combination, dosage and cumulative dose of the drugs depends on the risk-group and varies between the different study groups.
Figure 7. General flow chart for the treatment of non-orbital head and neck rhabdomyosarcoma (non-metastatic disease)

CT, chemotherapy; EBRT, external beam radiation therapy; PRE, primary re-excision; CCR, clinical complete remission; IRS, Intergroup rhabdomyosarcoma study

1. Feasibility of radical resection is determined by the likelihood of respecting a 1-2 cm margin of uninvolved tissue or a fascial plane, without inducing severe mutilation or functional impairment.

2. Patients with parameningeal disease > 1 jr receive routine EBRT (see text for details regarding timing, dose and portals).
   In patients with non-parameningeal disease, local treatment depends on response to chemotherapy, but all patients receive EBRT.
   If CCR is achieved, patients receive 41.4 Gy.
   In case of no CCR at week 17, delayed surgery (if feasible) is followed by EBRT (36 Gy after radical resection; 50.4 Gy after irradical resection).
   If delayed surgery is not feasible, patients receive EBRT (50.4 Gy).

3. In non-parameningeal T1-tumors of non-alveolar histology, EBRT is withheld; all other patients receive 36 Gy.
In the IRS trials, the combination of VAC has been the ‘backbone’ in the treatment of most patients. Chemotherapeutic treatment of all non-orbital HNRMS patients in IRS IV consisted of 8 courses of VAC or VAI or VIE (all patients were randomly assigned to one of these regimens) through week 23. Afterwards, 4 courses of VAC were given through week 46. A and E were withheld during radiotherapy. None of the regimens compared was superior to any other. The SIOP study group traditionally uses IVA (substitution of cyclophosphamide by ifosphamide). In the SIOP MMT 95 trial, only patients with microscopically completely resected T1-tumors of non-alveolar histology at non-parameningeal head and neck sites received 2 courses of VA in 9 weeks. All other patients were randomized to receive either IVA or an intensified six-drug regimen consisting of IVA and carboplatin, epirubicin and etoposide. Patients with cervical lymph node metastases and patients < 3 yr with parameningeal tumors received the six-drugs regimen without randomization. Generally, 9 courses were given in 27 weeks. The results from this trial are not yet available. In the CWS trials, primary multi-agent chemotherapy consisted of VACAdr (CWS81) and VAIAdr (CWS86). In CWS 1986, the duration depended on IRS-stage, varying between 2 cycles (2x3 courses) in 20 weeks (IRS group I), 3 cycles (3x3 courses) in 26 weeks (group II), and 5 cycles in 46 weeks (group III and IV). In group III and IV, poor responders after the first VAIA cycle switched to the PIAV drug combination, in which actinomycin-D was replaced by cisplatin. High-dose chemotherapy (with or without total body irradiation) and stem-cell rescue has been evaluated in patients with advanced-stage or metastatic disease. Most protocols have included the alkylating agent melphalan. The benefit of these high-dose regimens remains to be defined. Intrathecal chemotherapy, consisting of triple intrathecal medications (TIM) (methotrexate, arabinosylcytosine and hydrocortisone), together with prophylactic radiation of the craniospinal axis was introduced in the late 1970s for the treatment of patients with parameningeal HNRMS and one or more signs of meningeal involvement. The rationale for this treatment was the poor penetration of chemotherapeutic agents through the blood-brain-barrier. The use of TIM has been abandoned, because the agents were minimally effective and treatment was complicated by the occasional development of ascending myelitis, attributed to the combined effects of chemotherapy and radiation therapy.

In general, the response of RMS to chemotherapy is good and can vary from reduction in tumor volume, conversion of the tumor into microscopic residual disease, to total eradication of the primary tumor (see paragraph 1.8). Moreover, chemotherapy can control possible micrometastases. However, cure with chemotherapy as the sole form of treatment is unlikely in non-orbital HNRMS. As a consequence of the high relapse rate after chemotherapy in patients with non-parameningeal disease and the risk for CNS extension in children with parameningeal disease, application of local treatment is currently recommended for all patients with HNRMS. According to some authors, the need for extensive surgical procedures, wide radiotherapy portals and high radiation dose is reduced in good responders.
Chapter 1

1.7.3.2 Surgery

Primary resection

The role of primary surgical treatment in HNRMS has changed. In general, initial surgery should be limited to those cases in which microscopical complete excision can be likely achieved without severe functional or cosmetical damage. Resection is considered microscopically complete when it is possible to provide a margin of normal tissue, conventionally 1-2 cm, or a fascial plane surrounding the entire circumference of the tumor. As described earlier, diagnosis in HNRMS is usually made late in the course of the disease. Expanded lesions involving surrounding structures are frequently encountered (see paragraph 1.6.1). Primary surgery is often considered not feasible at parameningeal sites, due to size of the lesion, deep placement, close relation to adjacent vital structures, and compact and complex anatomy of the head and neck region. The feasibility is higher in case of non-parameningeal disease. Complete resection (Clinical Group I, by IRS nomenclature) is achieved in 0-7% at parameningeal- and 9-24% at non-parameningeal sites. If primary resection is not feasible, surgery should be limited to biopsy only. Debulking procedures or partial excisions have no benefit over biopsy alone.

Primary re-excision

Primary re-excision (PRE) should be considered in case of positive margins, if achieving microscopic radicality is possible and non-mutilating. Successful PRE diminishes the incidence of local recurrence and could eliminate the need for postoperative irradiation, which is especially important in young children.

Delayed resection

Head and neck lesions not amenable for primary surgery are managed with biopsy, followed by neo-adjuvant chemotherapy and definitive local treatment (fig. 7). Delayed surgery as definitive local treatment for residual tumor can be considered (1) after sufficient reduction of the tumor by chemotherapy and (2) as a salvage procedure in case of incomplete response after chemoradiation (see paragraph 1.7.4). Second look surgical procedures performed to verify clinical complete remission alone (and withholding local treatment in patients having no vital tumor), proved to be inappropriate. Local relapse rates in up to 50% of the ‘tumor-negative’ patients were encountered. The feasibility of delayed tumor resection after chemotherapy has been reported in several (small) patient series, even in parameningeal disease. In most protocols, however, local treatment in parameningeal disease consists of early radiotherapy. The only exception to this ‘rule’ are patients younger than 2-3 years of age, who are at considerable risk for late toxicity following radiotherapy. The feasibility of delayed resection instead of radiotherapy is often considered in non-parameningeal disease. In the SIOP MMT 95 study, this occurs at week 18 (after 6 courses) and in the ongoing IRS V trial at week 12. In December 2000,
the guidelines of the SIOP MMT protocol were adjusted and prescribed (low-dose) radiotherapy following delayed surgery, even in case of radical resection (see paragraph 1.7.3.3). Evolution of craniofacial and skull-base surgery has improved access to difficult sites. Together with new developments in surgical reconstruction, this allows for increased possibilities of delayed resection. However, craniofacial approaches reported in parameningeal disease are often extensive surgical procedures (lateral temporal bone resection, infratemporal skull base approach, partial mandibulectomy, maxillectomy), carrying a substantial risk for damage to cranial nerves, craniofacial asymmetry, trismus, CSF fistula and meningitis.

Neck dissection
Regional failure in patients with uninvolved neck nodes at diagnosis is rare (see paragraph 1.8). Prophylactic treatment of ‘N0-patients’ is therefore not recommended. Tumorpositive cervical lymph nodes are irradiated (see paragraph 1.7.3.3). The only possible indication for neck dissection is for patients < 3 years, with a relative contraindication for radiotherapy.

1.7.3.3 Radiotherapy
RMS is sensitive to ionizing radiation. This sensitivity is reported to vary from moderately radiosensitive to radiocurable. External beam radiation treatment (EBRT) plays an important role in the treatment of HNRMS. Radiotherapy is indicated in all patients with parameningeal HNRMS and all patients with alveolar histology, irrespective of clinical group. In non-parameningeal RMS, application of EBRT depends on clinical group and histology. In patients with radically resected, T1-tumors of non-alveolar histology (Clinical group I), EBRT can be omitted. Until recently, EBRT was omitted for clinical group II and III patients when complete remission was achieved after chemotherapy with or without delayed resection, according to the SIOP and CWS guidelines. The current guidelines, however, recommend EBRT as definitive local treatment in all scenarios, as local control is significantly improved. The dose depends on response to chemotherapy, and completeness of a possible secondary resection (vide infra).

In the SIOP and ICS trials, radiotherapy was contraindicated in patients < 3 years, due to the considerable risk for the development of late sequelae (see paragraph 1.9). In CWS 86, radiotherapy was withheld in patients < 2 years and between the age of 2 and 3, decisions were made on a case-by-case basis. In IRS IV, there was no age limit for the application of radiotherapy. The new ESSG guidelines recommend EBRT in all parameningeal RMS patients > 1 year of age. Patients between 1-3 years of age with non-parameningeal RMS receive EBRT only in case of residual disease after chemotherapy.

Radiotherapy is delivered using megavoltage (4-20 MV) linear accelerators. Conventionally, photon
beams are used. Electron therapy can be given in superficial and moderately infiltrating tumors (to a maximum depth of 5 cm). Also, tissue-sparing charged particle radiotherapy (proton beam) can be applied in some cases. Treatment planning can consist of traditionally opposing lateral or wedged fields or cone down/shrinking fields. Newer methods for treatment planning include 3D-conformal and intensity modulated radiation treatment (IMRT) using computer-driven multileaf collimators. These newer techniques are extremely useful in the (parameningeal) head and neck region, where numerous critical structures are in the vicinity of the target volume. The chemotherapeutic agents actinomycin-D, doxorubicin, or etoposide are withheld during radiotherapy. The different study groups vary with respect to timing, dose, fractionation and clinical target volume of EBRT.

**Timing**

The optimal timing for initiation of EBRT is not clearly defined. Theoretically, in the setting of bulky, unresectable disease, RT should be given as early as possible to optimize local control. Traditionally, the SIOP-group preferred to continue chemotherapy in case of a sustained response. EBRT was either postponed (with a reduction of the size of the treatment portals) or eliminated whenever possible. This approach was associated with a higher local relapse rate, but, for specific sites, survival was not adversely affected due to effective salvage therapy.

The IRS philosophy was the opposite and recommended early radiation therapy. In a CWS study, the continuous complete remission rate was best in patients receiving EBRT before week 15. Jaffe and co-workers found that a delay of definitive local treatment had an adverse effect on survival only when local treatment was given after 20 weeks. In a study of 13 patients with group III and IV parameningeal disease, the timing of EBRT, ranging between 12-29 weeks from diagnosis, had no influence on local control. To our knowledge, no firm conclusions can be drawn from the papers dealing with the issue of timing of EBRT. Timing is merely chosen on an empirical basis, because in most of the patients a satisfactory response has been achieved after 6-9 weeks. For most patients in IRS IV, radiation commenced at week 9 (range 9-18.5 weeks). For patients with parameningeal disease and high-risk features, RT was scheduled in week 1. In the SIOP MMT 95 protocol, EBRT was given in week 9 for patients with parameningeal RMS and poor responders of the 'six drugs' arm. For other patients, RT was timed in week 18, or at any given time during disease progression. In CWS 86, RT was timed in week 10-13. The new ESSG guidelines recommend that the possibility for delayed surgery must be checked before the onset of RT. In patients receiving no delayed surgery, RT is scheduled in week 12. In case of delayed surgery, RT starts within 21 days after surgery.
Dose
Radiation dose depends on clinical group and histology. General recommendations prescribe at least 40 Gy for eradication of microscopic residual disease and 50 Gy for macroscopic residual disease. Some authors claim that doses less than 40 Gy can be given for microscopic residual disease. When electron therapy is used, a maximum dose of 40 Gy is given because of the risk of radiation dermatitis. In IRS IV, group I alveolar and group II patients were treated with 41.4 Gy and group III patients with 50 Gy (conventional fractionation) or 59.4 Gy (hyperfractionation). Dose limits were set to critical structures such as the optic nerve and chiasm (46.8 Gy), spinal cord (45 Gy), lacrimal glands (41.1 Gy) and lens (14.4 Gy). In the SIOP MMT 95 study, 45 Gy was given in standard fractionation, with or without a boost of 5 Gy in 3 daily fractions. An increased boost of 10 Gy in 6 daily fractions was recommended in patients with macroscopical residual disease. A recent change in guidelines (in December, 2000) recommended 36 Gy in case of microscopic residual disease or CR. The latest ESSG recommendations for clinical group I and II patients are the same as those of IRS IV. For clinical group III patients, the dose depends on response to chemotherapy and feasibility and completeness of delayed resection. When complete remission is achieved with chemotherapy without delayed surgery, 41.4 Gy is given (50.4 Gy for alveolar tumors). In case of complete secondary resection following chemotherapy, patients receive 36 Gy (41.4 Gy for alveolar tumors). When delayed resection is not feasible or incomplete, the dose is 50.4 Gy, independent of histology. The radiation dose for treatment of the craniospinal axis is 36 Gy for patients > 3 years of age and 24 Gy for patients 1-3 years of age (vide infra). The dose to tumorpositive lymph nodes is 41.4 Gy if no enlarged lymph nodes persist after chemotherapy. In case of persisting nodes, 9 Gy is added.

Fractionation
In the SIOP study, treatment is applied using conventional fractionation, e.g. 1.8 Gy daily. This fraction size can be reduced in case of large treatment portals or young age (< 3 years). In hyperfractionated radiation therapy, fraction size is further reduced (1.2 Gy) and the number of fractions is increased (twice daily). This results in an increased total dose while overall treatment time is unchanged. According to radiobiologic theories, a small fraction size would allow preferential repair of sublethal damage to cells with a low turnover rate (normal tissues) compared to tumor cells. As fraction size is the factor which contributes the most to late effects, increasing the total dose and reducing the fraction size would give an improved local control rate without increasing late morbidity. However, to date, no studies with an adequate follow-up have reported improved local control rates.
Clinical target volume
The IRS advocates radiotherapy to the pre-treatment volume (as delineated by MR imaging at diagnosis) plus a 2 cm margin in all patients. In case of parameningeal disease, this concerns the pre-treatment volume plus 2 cm of the adjacent meninges. In former IRS trials, radiation of the craniospinal axis and TIM were recommended for all parameningeal HNRMS patients with high-risk features. There is, however, no evidence that eliminating whole brain XRT and TIM adversely affects survival of those patients.\textsuperscript{239} To date, the only indication for radiation of the entire craniospinal axis is intracranial extension of the disease and positive CSF cytology.\textsuperscript{234,239} The SIOP guidelines for parameningeal disease are comparable. Disseminated meningeal disease or tumor cells in the CSF are the only indications for radiotherapy of the whole craniospinal axis. In case of skull base erosion or cranial nerve palsy without intracranial tumor extension, the CTV is set to the primary tumor including the skull base of the involved cranial fossa and immediate adjacent fossa (i.e. the whole skull base when the middle fossa is involved). When there is additional intracranial extension of the tumor, the CTV includes the initial intracranial component plus a 2 cm margin; the skull base is included as outlined above. In non-parameningeal HNRMS the clinical target volume (CTV) was restricted to the residual tumor area (including a safety margin of 2-3 cm if feasible) in case of incomplete response after initial chemotherapy. Recently, the SIOP guidelines changed to include the initial tumor volume.

1.7.3.4 Brachytherapy
Brachytherapy (BT) is not routinely applied in HNRMS. BT, by implanting radioactive sources into the tumor bed, can deliver a high and focused dose to the target area, with a rapid fall-off of the dose outside the implanted volume. Therefore, the radiation dose to healthy surrounding tissues is diminished. Consequently, acute toxicity and late sequelae can be reduced when compared to standard teletherapy. Thus, BT can be an excellent alternative to EBRT or can be given as a boost supplement to EBRT. Experience with BT in the treatment of pediatric soft-tissue sarcoma exists in a few centers.\textsuperscript{240-242} Several studies report on the feasibility of BT following surgery. The method used most commonly is temporary interstitial implantation, i.e. the placement of hollow catheters at the time of surgery which are subsequently loaded with active sources a few days after surgery. Both low-dose rate (0.4-2 Gy/h) and high-dose rate (> 12 Gy/h) techniques have been used.\textsuperscript{243} Many reports consist of the pooled analysis of heterogeneous groups of patients with respect to site and histology of the tumors.\textsuperscript{241,243-245} Experiences with BT for RMS are described at urogenital sites and the extremities.\textsuperscript{246-248} Results are reported as favourable with limited sequelae, especially in low-dose rate techniques. Experiences with BT in HNRMS are reported in cases or small series of patients, and mainly concern localized tumors at non-parameningeal sites (including the orbit).\textsuperscript{240,242,249,250} Very few parameningeal tumors have been treated with BT.\textsuperscript{242}
1.7.4 Salvage strategies

General guidelines for local salvage of refractory or local recurrent HNRMS include a combination of second-line chemotherapy and radiotherapy and/or surgery when possible. Salvage strategies are individualized, depending on the upfront treatment already received.

The SIOP MMT 95 protocol advocates a minimum of six courses of second-line chemotherapy. The drug choice depends on initial chemotherapy. Fair responses are reported with etoposide, melphalan, carboplatin, etoposide, MTX given as single agents or in combination, cyclophosphamide plus topotecan, and thiotepa. To overcome the problem of multidrug resistance, there is a possible role for so-called ‘multidrug resistance modulators’. Intensive chemotherapy (high-dose or megatherapy) with alkylating agents and hematopoietic stem-cell rescue has been attempted to improve the results. The prognostic benefit of this strategy is, however, still unproven.

EBRT can be applied if not already given as first-line treatment. A renewed course of EBRT would exceed the radiation tolerance of normal tissues and is usually considered impossible, even with conformal techniques. In selected pediatric cases with no surgical options, re-irradiation should be considered. Recently, the application of IMRT has been described in adult patients with recurrent head and neck cancer. This form of treatment might also have a role in the re-irradiation of children. Again, brachytherapy can be an excellent alternative to EBRT and has been applied in adult extremity soft-tissue sarcomas with good local control rates. Very few studies report on the feasibility of BT in pediatric patients with recurrent disease. Salvage surgery offers the best chance for cure. However, the achievement of healthy margins is often not possible and will lead to unacceptable cosmetic and functional consequences.

1.7.5 Novel and experimental therapy

Newer drugs like topotecan, irinotecan, taxotere and taxol are being examined for their potential role in the treatment of RMS. Inositol hexaphosphate (IP6), a phosphorylated carbohydrate that is present in almost all human cells (and possesses a regulatory role in cellular proliferation and differentiation), can inhibit human RMS cells in vitro and in vivo. Cyclin-dependent kinase (CDK) modulators can influence the cell-cycle and induce apoptosis in RMS cell lines. Anti-angiogenetic agents, for example antibodies to vascular endothelial growth factor, have shown to inhibit RMS cell growth in animal models. Peptides derived from the PAX3/FKHR fusion protein could have a possible role as tumor antigens for cytotoxic T-lymfocytcs (immunotherapy).
1.8 Outcome in head and neck rhabdomyosarcoma

The results of treatment of patients with HNRMS are either reported as a part of the large multicenter trials (IRS, SIOP, CWS) or as consecutive single-center series, making it difficult to compare the outcome of the various studies. Single-center studies often comprise retrospective, small series, frequently report over large time intervals and lack uniform treatment. Multicenter trials traditionally had important differences with respect to (1) tumor staging, (2) histologic classification, (3) therapeutic strategies (4) distribution of prognostic factors (site, stage and histology) within groups and (5) definition of outcome measures. With the evolution of treatment protocols, attempts have been made to unify classification systems. In general, the large consecutive trials have reported a gradual improvement in outcome throughout the years. The differences between treatment strategies have become smaller.

In irresectable HNRMS at diagnosis (clinical group III, according to IRS nomenclature), the response to initial multidrug chemotherapy is good. In general, a 50% decrease in tumor volume can be achieved. Complete remission with chemotherapy as the sole form of treatment has been described in 38-40% of the patients with parameningeal HNRMS and in 30-38% of the patients at heterogeneous sites. However, there is growing evidence that cure with chemotherapy alone is unlikely, as relapse rates are unacceptably high in the absence of local treatment. Thus, consolidation of the response achieved with chemotherapy by appropriate local treatment seems mandatory.

With the use of risk-based multimodality treatment protocols, a complete remission can be achieved in 84-88% of all non-parameningeal- and 68-84% of all parameningeal HNRMS patients. Some 26-33% of the patients experience recurrent disease. In 58 to 84% of the relapsing patients, local recurrent disease is involved. A pure local relapse is seen in 38% of the relapsing patients, 27% of the relapses in parameningeal disease occur in the CNS and 10-30% develop distant metastases. There is a remarkably low incidence (2-6%) of regional (nodal) failure. The survival rates of patients with non-orbital HNRMS are summarized in Table 6. In general, the range for overall survival (OS) at five years is 70-80% for non-parameningeal, and 50-70% for parameningeal HNRMS (Table 6). The results from the most recent IRS study (IRS IV) show promising EFS and OS rates. Reports from the European groups of the same era are not yet available.

Survival for the patients who experience disease progression or relapse is very poor. A 0-34% long-term survival for these patients is reported. A recent paper, however, reports a 60% 5-year survival in 8 patients feasible for salvage surgery out of 11 incomplete responders to chemoradiation.
1.9 The late sequelae of external beam radiation therapy in the head and neck region

With the application of combined modality treatment protocols, the number of children surviving HNRMS has increased, but the increased cure rates have been achieved at a price. The experience with combination therapy has now reached sufficient follow-up time to document complications in long-term survivors. Late toxicity as a consequence of treatment of HNRMS is a common phenomenon: some 77-100% of the patients suffer from one or more sequelae, varying in severity. Although all treatment modalities (surgery, chemotherapy and EBRT) and even the effects of the tumor itself or supportive care can contribute to this late toxicity, most of the late sequelae in the head and neck region are thought to be secondary to EBRT.

The incidence, extent and severity of radiation-induced sequelae depends on age of the patient.
radiation energy (source), radiation dose, fraction size, treatment portals and previous and concomitant therapy (surgery and chemotherapy). Children with HNRMS are extremely susceptible to the late sequelae of EBRT for several reasons: (1) the young age at the time of diagnosis; as dividing cells are the main target for radiotherapy, the difference in toxicity to tumor- versus healthy cells (therapeutic ratio) is lower in young children, and maturing tissues in the head and neck such as the brain, skull and facial musculature have a substantial risk for morbidity, (2) the close proximity of structures in the head and neck region; many important radiosensitive structures such as the optic nerve, eyes, salivary glands, brain and spinal cord are in the vicinity of the tumor, (3) the large treatment portals, encompassing the initial tumor volume plus a safety margin and (4) the high radiation doses (50-60 Gy) given.

1.9.1 Overview of the late sequelae in children after treatment for HNRMS
As stated, late toxicity is encountered in 77-100% of the surviving HNRMS patients. An overview of the different manifestations of late toxicity is given in Table 7. In this table, late toxicity is categorized into the following main groups: auditory/hearing, craniofacial/dental/occlusional, dermatology/skin, endocrine, gastro-intestinal, musculosekeletal, neurologic, ocular/visual and secondary malignancy. Specific chemotherapy-induced toxicity is not included.

1.9.2 Radiation-induced growth disorders of the craniofacial skeleton
One of the most common and invalidating sequelae of EBRT is the radiation-induced growth suppression of the craniofacial skeleton (fig. 8). This growth suppression results in an asymmetrical craniofacial appearance in as many as 59-97% of the irradiated HNRMS patients. Next to anatomic and physiologic deficits, this sequel often leads to major psychological problems. Reconstructive surgery (osteotomies and bone-grafting) is difficult and often consists of extensive and repetitive procedures with compromised wound healing as a consequence of post-irradiation ischemia.

1.9.2.1 Normal craniofacial growth
In the postnatal growth of the craniofacial complex (viscerocranium) a variety of mechanisms are important: (1) bone remodelling via apposition and resorption at almost all periostal surfaces (including the vertical drift in the alveolar sockets), (2) enchondral ossification in the mandibular condyl, the synchondrosis sphenoid-occipitalis and, to a lesser extent, the cartilagenous nasal septum, (3) intramembranous ossification in the sutures and (4) growth following displacement of bony surfaces. Craniofacial growth is under control of systemic (genetic, hormonal and nutritional) and local influences and is still not completely understood. A widely accepted theory states that stimuli exerted by the growth and actions of surrounding structures (the functional matrix) act as the major initiating factors instead of intrinsic genetic programming of bone tissue.
Table 7. Overview of the late sequelae in children after treatment for HNRMS

1. Auditory/ hearing
   - External auditory canal
     - External otitis
     - Necrosis of the canal soft-tissue or bone
   - Inner ear/ hearing
     - Sensorineural hearing loss
     - Tinnitus
   - Middle ear/ hearing
     - Serous otitis
     - Chronic otitis media/ mastoiditis
     - Conductive hearing loss

2. Craniofacial/ Dental/ Occlusional
   - Craniofacial
     - Bony hypoplasia/ facial asymmetry (orbit/midface/mandible)
     - Velopharyngeal incompetency
   - Dental
     - Tooth agenesis (anodontia/hypodontia) (missing teeth)
     - Arrested root development
     - Root malformation (shortening, blunting, thinning, tapering)
     - Microdontia
     - Altered eruption pattern
     - Premature closure of apices
     - Enamel defects (hypoplasia/ hypocalcification)
     - Radiation caries
   - Occlusional
     - Trismus
     - Temporomandibular joint dysfunction
     - Malocclusion

3. Dermatology/ skin
   - Dry skin/ atrophy
   - Pigmentation changes
   - Radiation dermatitis
   - Wound infections

4. Endocrine
   - Decreased growth velocity (hypopituitarism)
   - Hypothyroidism (primary)
   - Other (pubertas praecox)

5. Gastro-intestinal
   - Anorexia
   - Dysphagia
   - Fistula
   - Xerostomia/ hyposalivation (mouth dryness)
   - Mucositis due to radiation
   - Stomatitis/ pharyngitis
   - Salivary gland changes
   - Altered sense of smell
   - Taste disturbance (dysgeusia)

6. Musculoskeletal
   - Osteo/ chondronecrosis
   - Osteomyelitis
   - Soft tissue fibrosis/ atrophy

7. Neurologic
   - Cognitive disturbance/ learning problems
and cartilage growth plates.\textsuperscript{293} The existence of certain vital growth centers has become less plausible.\textsuperscript{291} Craniofacial growth is the composite of different growing units (nasomaxillary complex, mandible, skull base and zygoma/orbit) and the growth of each unit has a different rate and duration.\textsuperscript{292,294}

1.9.2.2 Influence of radiation on craniofacial growth

The influence of radiation on craniofacial growth is exerted both directly and indirectly. Radiation interferes directly with subperiostal bone formation by osteoblasts and proliferation of chondroblasts (affecting regions of enchondral ossification) and causes fibrosis of marrow spaces.\textsuperscript{295} The indirect influence consists of compromising the supporting vascular bed by damaging its endothelial lining.\textsuperscript{282,296,297} Moreover, cicatrization and fibrosis of the adjacent soft tissues (functional matrix) and maldevelopment of the teeth cause interference with the natural stimulus for growth of the underlying bone.\textsuperscript{298} Craniofacial growth is also influenced by concomitant chemotherapy and radiation of the hypothalamic-pituitary axis.\textsuperscript{299}

Radiation doses sufficient to cause bony growth retardation are in the range between 4 and 30 Gy.\textsuperscript{283,298,300,301} The sites at which enchondral ossification occurs (the mandibular condyl and the synchondrosis spheno-occipitalis) are affected by lower doses (4-4.5 Gy).\textsuperscript{299} Cicatrization of the soft-tissues (functional matrix) can occur after radiation doses of 4 Gy.\textsuperscript{300} Some studies failed to demonstrate a relationship between age at the time of irradiation and growth retardation.\textsuperscript{300} Other studies come to different conclusions regarding the age before which children are most sensitive to radiation-induced growth suppression: 5 years of age\textsuperscript{301}, 6 years of age\textsuperscript{295,302,303} and 9 years of age.\textsuperscript{274}

The interval between radiation and the appearance of sequelae is related to the mitotic activity of the tissue involved. In tissues with a slow turn over rate, such as bone, the impact of radiation on growth may take years. In many case series of children with malignancies in the head and
neck region, mainly based on clinical observation and roentgencephalometric analysis, the appearance of craniofacial growth disorders is reported 2-3 years after EBRT. However, the growth deficits are not yet fully expressed until the patient has attained final height. Growth suppression is not restricted to the portion of the craniofacial skeleton within the portals of radiation treatment, but frequently affects multiple levels (orbit, midface and mandible). Attempts to prevent radiation-induced growth inhibition of EBRT have included (1) reduction of radiation dose in selected cases, (2) hyperfractionation, (3) proton beam radiation, (4) improved dosimetry, e.g. shrinking field technique, three dimensional conformal radiation therapy, intensity modulation techniques and (5) preventive measures, like hyperbaric oxygen therapy and radiation response modifiers. To date, the reports concerning a decrease in growth disorders after treatment according to new techniques are still lacking. However, it is known that brachytherapy, due to its tissue-sparing capabilities, can preserve bone growth and function.
Chapter 1

2. Dilemmas in the local treatment of head and neck rhabdomyosarcoma and rationale for the AMORE protocol

Pediatric HNRMS remains a challenging disease for the treating physicians. Despite the increasing efficacy of current treatment protocols, there are still dilemmas in the treatment of HNRMS.

Primary treatment

In summary, HNRMS affects young children (paragraph 1.1) and is a high-grade malignant tumor associated with aspecific initial symptoms (paragraph 1.4). Therefore, diagnosis is generally made late in the course of the disease, resulting in locally advanced tumors at diagnosis (paragraph 1.6). The head and neck area, especially at parameningeal sites, has a complex and compact anatomy and is cosmetically important. Due to the size and the site of HNRMS, radical primary surgery is often not possible without severe functional and/or cosmetic consequences (paragraph 1.7). Good response rates are achieved with initial chemotherapy, but local tumor control (and therefore local treatment) remains of vital importance (paragraph 1.7). Most protocols recommend routine EBRT in all patients, except after radical resection of non-alveolar T1-tumors at non-parameningeal sites (paragraph 1.7). Radiation treatment portals encompass the initial tumor volume plus a 2 cm margin. Therefore a large part of the head and neck area is exposed to (high-dose) ionizing radiation and many radiosensitive normal tissues are in close proximity, especially in small children (paragraph 1.9). Moreover, growing tissues (e.g. bone) are extremely susceptible to radiation-induced damage (paragraph 1.9). Consequently, EBRT results in numerous sequelae in the majority of the patients (paragraph 1.9). Microscopically radical resection following initial chemotherapy (delayed surgery) can eliminate the need for EBRT, but is often mutilating. Thus, the best way of using and combining the major modalities in primary local treatment to achieve optimal tumor control with minimal treatment-induced late sequelae is still not clear.

Salvage treatment

In a considerable number of patients, clinical complete remission can not be achieved (paragraph 1.8). The need for further local treatment in case of ‘radiological’ residual disease after chemoradiation remains unclear. None of the methods available for the assessment of complete response (CT/MR imaging, PET-scanning and tissue sampling) is 100% reliable in predicting the presence of viable tumor cells. However, a high (75%) relapse rate is found in patients with radiological residual disease. Options for salvage treatment of patients who experience disease progression or relapse are very limited (paragraph 1.8). Chemosensitivity is often reduced due to acquired drug resistance. A renewed course of EBRT would exceed the radiation tolerance of normal tissues and is usually considered impossible (paragraph 1.7). As a consequence, the outcome is very poor (paragraph 1.8). Promising local control rates can be achieved with salvage surgery, if feasible.
Rationale for the AMORE protocol
Despite the gradual improvement in outcome in HNRMS, reports of diminished late sequelae in primary treatment (even with the use of modern radiotherapy techniques) or effective salvage strategies are lacking. Brachytherapy, although applied in small series of patients, is reported to be effective and tissue-sparing and can even be applied in regions formerly treated with EBRT (paragraph 1.7).

In 1993, the AMORE protocol was developed in the Academic Medical Center. AMORE is the acronym for Ablative surgery, MOulage-technique brachytherapy and surgical REconstruction. AMORE combines tissue-sparing surgery, aiming for macroscopically complete resection of the residual (post-chemotherapy) tumor mass, with brachytherapy for the eradication of possible microscopic residual disease and surgical reconstruction for restoration of function and contour. This strategy was developed to optimize local control and to avoid the late sequelae of external beam radiation treatment. AMORE has been applied both as primary local treatment and salvage treatment for children with non-orbital HNRMS.

3. Aims and scope of the thesis
In this thesis, the series of non-orbital HNRMS patients treated according to the AMORE protocol are evaluated with respect to the following issues:

(1) outcome in both primary and salvage treatment;
(2) treatment-induced sequelae, with an emphasis on craniofacial growth;
(3) identification of factors associated with local failure, and
(4) recommendations for future in- and exclusion of patients and improvements of the protocol.

After a description of the methods of the AMORE protocol, these issues are dealt with in the subsequent chapters.
References

General introduction


86. Davis RI, D'Cruz CM, Lovell MA, Biegel JA, Barr FG. Fusion of PAX7 to FKHR by the variant t(1;13)(p36;q14) translocation in alveolar rhabdomyosarcoma. Cancer Res 1994;54:2869-2872.


General introduction


Chapter 1


Chapter 1


