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DENTAL LATE EFFECTS IN SURVIVORS OF CHILDHOOD CANCER

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BSc (Hons) DDS (Hons) (Mahidol)

A thesis submitted in partial fulfilment of the requirements for the degree of

MASTER OF DENTAL SCIENCE (Paediatric Dentistry)

Faculty of Dentistry
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University of Sydney

December 1994
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ABSTRACT

Advances in treatment of childhood malignancy have resulted in an increasing number of long-term survivors. This success has now directed increasing attention to the sequelae (or late effects) and the quality of life of the survivors. The objectives of this study are to describe dental late effects in the survivors of childhood cancer and relate these findings to varying parameters such as diagnosis, age at beginning of therapy, and treatment protocol.

Two hundred and one survivors of childhood cancer, followed up at the Late Effects Clinic at the Royal Alexandria Hospital for Children, Camperdown, Sydney, were evaluated dentally for treatment related adversity. The assessment included clinical and panoramic radiographic examinations. The patients were classified into three major groups: cranial irradiation, head and neck irradiation and chemotherapy. The variables studied are oral health status (dental caries and periodontal status), facial deformity, trismus, occlusion, orthodontic treatment need, dental maturity, and dental developmental abnormalities.

The mean of age at examination of the patients was 10.4 years, the median age was 9.9 years, and the majority (58%) were male. The results showed no difference in oral health status among the three groups. Facial deformity and trismus presented significantly more often in the head and neck irradiation group (p<0.0001). Requirements for orthodontic treatment were not different among the three groups. Dental maturity was significantly greater than chronological age in the cranial irradiation group (p<0.0001), but no difference was found in the other two groups.

The head and neck group had the most severe dental developmental abnormalities while the chemotherapy group exhibited the least severe problems. The highest number of affected teeth was also found in the head and neck irradiation group. Shortening of roots was the most common developmental abnormality in these patients. The distribution
pattern of dental abnormalities in these three groups was different. Children, younger than 6 years of age at the commencement of treatment, showed more severe dental abnormalities than those older (p<0.0001). Focusing on the cranial irradiation group, dental abnormalities displayed greater severity in patients who received 2400-cGy radiation dose and LSA2-L2 chemotherapeutic protocol than in BFM and other chemotherapeutic protocol. Severity of dental developmental disturbance was also associated with medical complications which are not uncommon in these patients.

The findings suggest that oral health status of long-term survivors of childhood cancer is probably within normal range. Attention to oral health care, however, remains necessary due to existence of a variety of other dental late effects which may place these patients at higher risk for oral diseases. Dental late complications vary mainly with the age at beginning treatment and treatment modality. They also suggest the presence of other medical complications. It is proposed that the severity of dental complications may be used as a strong indicator for the likelihood of other late effects. Good collaboration between dental and medical personnel, and within the dental profession, is essential so that these consequences can be minimised.
STATEMENT OF AUTHORSHIP

This study was carried out at the Late Effects Clinic, Oncology Unit at the Royal Alexandra Hospital for Children, Camperdown and at Westmead Hospital Dental Clinical School, Sydney, between June 1992 and October 1994. This work has not been submitted in whole or in part for any other degree.

Results from various aspects of this research have been presented at the following scientific meetings during the course of study.

Australian and New Zealand Society of Pediatric Dentistry
9th Biennial Conference
May, 1993- Perth
Oral presentation

International Association for Dental Research
(Australian and New Zealand Division)
34th Annual Scientific Meeting
September, 1994- Melbourne
Oral presentation
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I was privileged to be supervised by Professor Peter Barnard, Head of Preventive Dentistry, and Dr Richard Widmer, Head of Paediatric Dentistry at Westmead Hospital. Professor Peter Barnard has taught me much about dental research. Dr Richard Widmer suggested this topic and introduced me to the field of oncology. I wish to deeply thank both of these supervisors for their tireless encouragement, supportive attitude and friendly guidance during this study.

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I owe my sincere thanks to Miss Doungkamol Sindhusake for performing the meaningful statistical analyses. I am indebted to Mrs Frances Porter for her friendship and secretarial assistance. Mrs Mara Cvejic of the Research Support Unit in the Dental Clinical School and the Audio Visual Department at Westmead Hospital were of great assistance with preparation of photographs.

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<td>ALL</td>
<td>Acute lymphoblastic leukaemia</td>
</tr>
<tr>
<td>ANLL</td>
<td>Acute nonlymphocytic leukaemia</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BMT</td>
<td>Bone marrow transplantation</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>cGy</td>
<td>Centigray (1/100 Gray or 1 rad)</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray (1 joule of energy absorbed in 1 kilogram of tissue, 1 Gy is equivalent to 100 rad)</td>
</tr>
<tr>
<td>HTLV</td>
<td>Human T lymphotopic retrovirus</td>
</tr>
<tr>
<td>NHL</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>OPG</td>
<td>Orthopantomograph</td>
</tr>
<tr>
<td>R</td>
<td>Roentgen (a unit of exposure or ionisation produced in air, 1 R is roughly equivalent to 0.95 cGy in soft tissue)</td>
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<tr>
<td>RB</td>
<td>Retinoblastoma</td>
</tr>
<tr>
<td>RMS</td>
<td>Rhabdomyosarcoma</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SNS</td>
<td>Sympathetic nervous system</td>
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<td>WT</td>
<td>Wilms' tumour</td>
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CHAPTER ONE

INTRODUCTION

1.1 STATEMENT OF PROBLEMS

Childhood cancer is considered as a malignancy occurring before 15 years of life. In Australia, it is estimated to affect eleven in 100,000 children per year and occurs in males 50% more than in females (McWhirter and Masel 1987 p 4). Most childhood cancers are of mesodermal origin. Haematopoietic, central nervous system and lymphoid tumours are the most common cancer types in children (Fernbach and Vietti 1991).

Surgery, radiation therapy, and chemotherapy are the three major cancer treatment modalities, usually employed in combination, in modern paediatric cancer therapy. Bone marrow transplantation (BMT) is also now another established therapy for these patients. Thirty years ago few children in Australia survived cancer, therefore there were very few in whom the long-term effects could be studied. Nowadays, advances in treatment of malignancy in children have led to an overall survival rate of 60% (McWhirter, 1994). Meadow and others (1992) estimated that by the year 2000, one in every 1000 young adults in their third decade of life would be a survivor of childhood cancer. Whereas the decreased mortality rate is very encouraging, the morbidity associated with the treatment remains high. This has now guided attention of many health professions towards the long-term sequelae.

Since little information has been documented in the dental literature, questions often arise about the oral complications following paediatric cancer therapy. Oral health status and craniofacial and dental developmental abnormalities are the main areas of interest. Most previous studies, however, investigated some aspects of such complications. The overall picture for these patients remains unclear.
Introduction

The chronic effect of different types of cancer treatment on orofacial structures is another interesting study aspect. It has been, however, reported in only a few publications. Also attempts to compare these effects between different studies is difficult because of divergent study design. In addition, the accurate, quantifiable, and reproducible criteria for assessing and classifying oral complications of cancer therapy remains to be developed.

A Medline search using 10 different key words and personal contact with 3 experts in the field produced no previous studies on dental late effects in survivors of childhood malignancy in Australia.

1.2 OBJECTIVES

The aims of this study are to describe the dental late effects found in long-term survivors of childhood cancer and to investigate associations with related variables.

The objectives of this study are to:

- detect the caries level in the study population
- detect the prevalence of periodontal disease in the study population
- record facial deformity prevalence in the study population
- record trismus prevalence in the study population
- assess the patterns of occlusion in the study population
- assess dental maturity of the study population compared with their chronological age
- assess dental developmental anomalies in the study population
- determine the severity and distribution pattern of dental abnormalities in different groups of treatment
- relate the severity of dental anomalies to the child's age at the beginning of cancer treatment
- attempt to delineate the dose of radiation for the cranial irradiation group, at which the least dental damage occurs
- attempt to delineate which chemotherapeutic protocol for the cranial irradiation group leads to the least dental damage
- summarise the medical complications for the study population
- relate the severity of dental abnormalities to the severity of medical complications.
1.3 RESEARCH PLAN

In order to achieve the above objectives, this observational study is designed so as to permit the collection of all associated data from the target population. Criteria for determining study variables are defined after considering related constraints, such as time and availability of personnel. The data was directly entered into a microcomputer and data analysis completed with the aid of the SPSS/PC+ statistical package. A literature review covering childhood cancer, cancer therapy, dental development, and dental late effects in survivors of childhood cancer is also presented in this thesis.
CHAPTER TWO

LITERATURE REVIEW

2.1 CHILDHOOD CANCER

2.1.1 Introduction
The word "cancer" is derived from the Latin word for crab - it adheres to any part that it seizes upon in an obstinate manner like the crab. In general, cancer refers to malignant neoplasms. A neoplasm as defined by Willis, is "an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change" (cited by Kumar et al 1992 p 172). "Malignant", as applied to a neoplasm, implies that it can invade and destroy adjacent structures and spread to distant sites (metastasise) to cause death.

Dargeon (1960) mentioned that Egyptian records revealed the existence of benign and malignant tumours as far back as 1500 BC. The first authentic accounts of tumours in children, however, appeared only when Wandrop in 1809 mentioned 20 cases of malignant tumours of the eye in children under 12 years of age.

According to Robison (1993), the vast majority of vital statistics and epidemiologic data consider childhood cancers as those occurring before 15 years of age although from a clinical perspective the upper age for defining childhood cancer is debated.

Childhood cancer survivors are defined as the former childhood cancer patients who were cured. The criteria for cured childhood cancer patients, mentioned by Meadow and Hobbie (1986), include those who had survived for at least 5 years beyond their last evidence of disease and who had been off therapy for at least 2 years.
2.1.2 Comparison of Cancer in Children and in Adults

In addition to the low incidence, cancer in children differs from cancer in adults in many other ways (Table 2-1). Most of the childhood cancers are of mesodermal (92%) and, occasionally, ectodermal origin. Most of the malignant neoplasms of adults are of epithelial origin. Carcinomas are extremely rare in children, whereas they account for over 85% of tumours in adults. Haematopoietic, central nervous system and lymphoid tumours are the most common tumour types in children.

Paediatric tumours tend to be deep-seated in areas where they do not cause obvious abnormalities of function, therefore, they are not generally detected early. Many may attain massive proportions before they are noticed by parents or physician and almost 80% of patients have distant metastases when their diseases are diagnosed.

2.1.3 Racial-ethnic and Geographic Variations

There are striking differences in the incidence rate of all cancer between the ages of 0 and 14 years in various regions of the world (Figure 2-1). The highest rate reported was in Ibadan, Nigeria, where the annual incidence was 15.56 per 100,000, almost four times that of the Indian population of Fiji where the reported incidence rate was 3.97 per 100,000. Clearly, a number of possible explanations must be considered when interpreting this broad spectrum, including the quality of the medical care system to diagnose cancer, differences in the classification of various neoplasms, the thoroughness of the cancer surveillance and reporting system, the size of the population and the accuracy of the census, and the true occurrence of cancer among various populations.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Children's Cancers</th>
<th>Adult's Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sites</td>
<td>Involve tissues (i.e., Haematopoietic, lymphatic, CNS, SNS, muscle, bone)</td>
<td>Involve organs (i.e., breast, lung, colon, prostate, uterus)</td>
</tr>
<tr>
<td>Histology</td>
<td>Primary sarcoma (non epithelial)</td>
<td>87% are carcinoma (epithelial)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td>80% are disseminated</td>
<td>Local and regional</td>
</tr>
<tr>
<td>Screening tests</td>
<td>Urinary catecholamines for neuroblastoma, otherwise not effective or practical</td>
<td>Mammography, occult blood in stools, Pap smear, colonoscopy, self-examination</td>
</tr>
<tr>
<td>Early detection</td>
<td>Mostly accidental</td>
<td>Improved with education and screening</td>
</tr>
<tr>
<td>Response</td>
<td>Very responsive to chemotherapy</td>
<td>Less responsive to chemotherapy</td>
</tr>
<tr>
<td>Outcome</td>
<td>&gt;60% 5 year survival (all types), probably &gt;60% cure</td>
<td>&lt;50% 5 year survival (all types)</td>
</tr>
<tr>
<td>Prevention</td>
<td>Unlikely; reduce skin cancer risk (with sun blocking creams)</td>
<td>80% are preventable (primarily tobacco)</td>
</tr>
</tbody>
</table>
Within the specific diagnosis subgroups of childhood cancer international differences are apparent in the reported incidence rates (Robison 1993).

1. Acute lymphocytic leukaemia - higher rates are seen in China, Japan, United States, England and Europe with lower rates in Middle East and Africa.

2. Acute nonlymphocytic leukaemia - highest rates are reported from China (Shanghai), Japan and New Zealand with relatively low rates seen in the United States and Europe.

3. Hodgkin's disease - highest rates are found in adolescents and young adults from industrialised western countries; highest rates in children tend to occur in less developed countries. The highest overall rates are reported from the United States, Latin America, Africa and Israel.

4. Non-Hodgkin's lymphoma - highest incidence is reported from Africa, presumably representing Burkitt's lymphoma, with a lower rate seen in Japan (approximately half that of other countries).

5. CNS tumours - higher rates are reported in United States white children, Denmark and Sweden, with lower rates seen in areas of Asia and Africa.

6. Neuroblastoma - higher rates are seen in North America, Europe, Israel and Australia; generally lower rates are reported from Africa, Central and South America and Asia.

7. Retinoblastoma - overall a relatively small variation is seen in rates, but a marginally higher incidence is found in India and black Africans.

8. Wilms' tumour - the highest incidence rates are reported among United States blacks, in Finland and regions of France; the lowest rates are reported from Asia.

9. Bone sarcoma - higher rates of Ewing's sarcoma are seen in Spain and amongst Hispanics living in the United States, whilst lower rates are generally reported from Asia; higher rates of Ewing's sarcoma are seen in United States whites, New Zealand, Australia and areas of Europe; a very low incidence occurs in blacks, Japanese and Chinese.

10. Soft tissue sarcoma - higher rates are seen in Spain and United States whites and Hispanics, whereas lower rates are seen in areas of Asia, including Japan, China, India and the Philippines.
Figure 2-1  Incidence of cancer in children less than 15 years of age in selected regions of the world (Source: Robison 1993)

Figure 2-2  Knudson's two-mutation hypothesis
In all tumours, the same cell must undergo at least two mutations to become malignant, and the second mutation always occurs after conception. In sporadic nonhereditary tumour (right), the first mutation also occurs after conception. In hereditary tumour (left), the first mutation is in a germ cell, such that all body cells in the offspring have the first mutation. (Source: Mulvihill 1993).
2.1.4 Aetiology

Overall, relatively little is known about the epidemiology and aetiology of many childhood cancers, particularly with respect to environmental issues and the possible interaction between genetic and environment factors (ecogenetics). Thus acute leukaemia represents approximately 28% of all paediatric cancers, the bulk of the analytic epidemiologic research has focused on leukaemic patients. In contrast, much of the information regarding the genetic and molecular aspects of paediatric cancers has come from studies of the less common tumour types, such as retinoblastoma and Wilms' tumours (Robison et al 1991).

The analyses of Knudson (1976) on age distribution at diagnosis, comparing hereditary and non-hereditary retinoblastoma, were the basis of the two mutation hypothesis and became a conceptual milestone in studies of carcinogenesis in humans. This hypothesis proposes that two discrete mutational events, possibly at the same genetic locus, may be required to transform a normal cell into a cancer cell. Using this explanation, cancer may occur when a cell is homozygous for a specific mutated cancer gene. These genetic mutations may be either prezygotic or post zygotic. The second event is virtually always postzygotic. Prezygotic mutations, therefore, are of hereditary nature whereas postzygotic mutation may be environmental (Figure 2-2). Thus, individuals who have inherited a mutated "cancer gene" may have this defect present in all cells of the body, requiring the second event for the expression of malignancy. These second events may occur as the result of irradiation, chemical carcinogens, or an oncogenic virus. These individuals might be expected to develop a specific tumour with high frequency at multiple sites, usually at an age earlier than those requiring two separate postzygotic events. These observations are consistent with bilateral retinoblastoma.
2.1.4.1 Environmental factors

Ionising Radiation

No human carcinogen is better understood than ionising radiation. Besides clinical observations as early as 1902, large epidemiologic studies document the carcinogenicity of radiation in children (Mulvihill 1993). Types of irradiation and various host factors may influence the dose-response curve, as does the individual sensitivity of specific tissues to irradiation carcinogenesis. It is for this reason that leukaemia and thyroid cancer are among the most easily induced radiation-associated malignancies and children are generally more susceptible than adults. An increased incidence of cancer has been observed in the survivors of atomic bomb irradiation in Japan with the highest incidence being in those younger than 15 years at the time of exposure. Breast and thyroid carcinoma and acute leukaemia were seen in excess to that of the normal population (Pratt 1985). Radiation therapy is also associated with the development of malignancy. An example is the increased incidence of thyroid cancer after external irradiation to the head and neck. There may be some risk of radiation-associated carcinogenesis following prenatal irradiation, yet there is no evidence of increased risk of malignancy following routine pelvic radiographs or in utero exposure to atomic bomb irradiation (Altman and Schwartz 1983). Prudent use of dental radiation is highly unlikely to cause harm (Wall et al 1979).

Ultraviolet Radiation

Sunlight may cause skin cancer later in adult life when there is high exposure in childhood and adolescence. Although skin cancer is virtually absent in children without a genetic predisposition, children who have a genetic predisposition such as xeroderma pigmentosum or another congenital defect in DNA repair, are at increased risk of developing neoplasms (Behrman 1992).
Asbestos

Exposure to asbestos in childhood may cause mesothelioma after a latent period of 30 to 40 years. Risks of cancer in these individuals increase with age and with exposure to cigarette smoke (Pratt 1985).

Chemicals

At least 54 chemical agents have been identified as probable human carcinogens (IARC Working Group 1980). Intrauterine exposure to diethylstilbestrol carries an increased risk of clear cell adenocarcinoma of the vagina in daughters of women given this drug. In addition, exposed children of both sexes commonly have malformations of the genital tract. Diethylstilbestrol is currently the only proven human transplacental carcinogen known, although two cases of neuroblastoma have been reported in infants with foetal hydantoin syndrome, and another has been reported in a child with foetal alcohol syndrome (Behrman 1992).

Immunosuppressive agents administered following renal or other transplantation have been associated with an increased incidence of malignancy, particularly non-Hodgkin lymphoma. Treatment of aplastic anaemia (especially of the Fanconi type) with anabolic androgenic steroids has led to various liver tumours: hepatocellular carcinoma, hepatonia or hepatic adenonia. Chemotherapy for malignancy may result in second neoplasms, with a cumulative risk as high as 12% at 25 years (Behrman 1992).

Diet

There is an unexplained association between high fat intake, obesity and the development of cancers of breast, colon and uterus in adults. Speculation is rife as to whether dietary manipulation may prevent the development of cancer in later life, with emphasis on the possible prevention of colon cancer through a diet high in vegetable fibre. No convincing clinical data support such ideas at present (Behrman 1992).
Biologic Agents
Burkitt's lymphoma, nasopharyngeal carcinoma and X-linked lymphoproliferative syndrome are associated with Epstein-Barr virus infections including infectious mononucleosis. Leukaemia and lymphomas of T-cells are known to be associated with human T lymphotopic retroviruses (HTLV-I and HTLV-III). HTLV-I has been demonstrated to be the aetiologic agent of clinically aggressive adult T-cell leukaemia-lymphoma, whereas HTLV-III was isolated from patients with AIDS (Pratt 1985).

2.1.4.2 Genetic factors
Humans differ in susceptibility to cancer. Some individuals are prone to cancer because of a predisposing genetic lesion. Others may be less susceptible and are unaffected despite intense exposure to a carcinogen. In general, the fraction of persons who develop cancer after exposure to a carcinogen is small, e.g., approximately 0.1% of Japanese children exposed to 100 R from atomic bombing have developed radiation-associated leukaemia annually (Li 1982). Those affected may be genetically susceptible.

Cancer develops with unusually high frequency in persons with certain genetic diseases. Approximately 300 single gene disorders, representing nearly 10 per cent of reported genetic diseases in humans, have been associated with carcinogenesis (Mulvihill 1993). Many of the traits were selected for inclusion in Table 2-2.
# Literature Review

## Table 2-2

Selected single gene traits associated with childhood and adolescent neoplasia (Source: Mulvihill 1993)

<table>
<thead>
<tr>
<th>Gene Trait, Neoplasm, or Disorder</th>
<th>Inheritance Chromosome* (if known)</th>
<th>Associated Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phakomatoses</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>von Recklinghausen's neurofibromatosis 1</td>
<td>AD†; 17q11.2</td>
<td>Sarcoma, neuroma, schwannoma, meningioma, optic glioma, pheochromocytoma, nonlymphocytic leukemia</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>AD†; 9q11q</td>
<td>Adenoma sebaceum, periungual fibroma, glial tumours, rhabdomyoma of heart, renal tumour, lung cysts</td>
</tr>
<tr>
<td>von Hippel-Lindau syndrome</td>
<td>AD†; 3p</td>
<td>Retinal angioma, cerebellar hemangioblastoma, other hemangiomas, pheochromocytoma, hypernephroma, cysts, gliomas</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>AD</td>
<td>Angioma of numerous organs</td>
</tr>
</tbody>
</table>

**Nervous System**

| Retinoblastoma                    | AD†; 13q14                     | Sarcoma, pinealoblastoma, early radiogenic tumours |
| Neurofibromatosis 2               | AD†; 22q                       | Bilateral acoustic neuromas, meningioma, spinal neurofibroma |
| Neuroblastoma                     | AR; AD                         |                                                  |
| Macroencephaly                    | AD†                            | Ganglioneuroblastoma |

**Endocrine**

<p>| Multiple endocrine neoplasia 1 (Wermer's syndrome; MEN-1) | AD†; 11q13                    | Adenomas of islet cells, parathyroid, pituitary, and adrenal glands; malignant schwannoma; nonappendicadal carcinoid |
| Multiple endocrine neoplasia 2 (Sipple's syndrome; MEN-2) | AD†; 10p                      | Medullary carcinoma of thyroid, parathyroid adenoma, pheochromocytoma |
| Multiple mucosal neuroma syndrome | AD†; 10p                      | Pheochromocytoma, medullary carcinoma of the thyroid, neurofibroma, submucosal neuromas of tongue, lips, eyelids |
| Paraganglioma (chemodectoma)      | AD†                            | Pheochromocytoma |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Inheritance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma</td>
<td>AD†</td>
<td>Parathyroid adenoma, chief cell hyperplasia</td>
</tr>
<tr>
<td>Thyroid goiter and dyshormonogenesis, including Pendred's syndrome</td>
<td>AD</td>
<td>Benign goiter</td>
</tr>
<tr>
<td>Arrhenoblastoma-thyroid adenoma</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td><strong>Mesoderm (Soft Tissue)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevoid basal cell carcinoma syndrome (Gorlin's syndrome)</td>
<td>AD†q31</td>
<td>Basal cell carcinoma, ovarian fibroma, medulloblastoma</td>
</tr>
<tr>
<td>Leopard syndrome</td>
<td>AD†</td>
<td>Multiple lentigines</td>
</tr>
<tr>
<td>Gingival fibromatosis ± hypertrichosis or other anomalies</td>
<td>AD†</td>
<td></td>
</tr>
<tr>
<td>Juvenile fibromatosis</td>
<td>AR†</td>
<td>Multiple subcutaneous</td>
</tr>
<tr>
<td>Familial cutaneous collagenoma</td>
<td>AR</td>
<td>Multiple skin nodules</td>
</tr>
<tr>
<td>Multiple lipomatosis, sometimes site specific, neck or conjunctiva</td>
<td>AD†</td>
<td>Skin cancer</td>
</tr>
<tr>
<td>Goldenhar's syndrome</td>
<td>AR</td>
<td>Kipodermoid of conjunctiva, haemangioma</td>
</tr>
<tr>
<td>Macrosomia adiposa congenita</td>
<td>AR</td>
<td>Obese soon after birth, eosinophilia, adrenocortical adenoma</td>
</tr>
<tr>
<td>Multiple hamartoma (Cowden's) syndrome</td>
<td>AD†</td>
<td>Papillomatosis of lip; benign and malignant tumours of breast, colon and thyroid, meningioma</td>
</tr>
<tr>
<td><strong>Alimentary Tract</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial polyposis coli and Gardner's syndrome</td>
<td>AD†s5q 21</td>
<td>Carcinoma of colon; hepatoblastoma, intestinal polyps, osteomas, fibromas, sebaceous cysts, carcinomas of ampulla of Vater, pancreas, thyroid, and adrenal</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>AD†</td>
<td>Intestinal polyps, ovarian (granulosa cell) tumour</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>AR†</td>
<td>Brain tumour, intestinal polyposis</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>AD†</td>
<td>Carcinoma of pancreas</td>
</tr>
</tbody>
</table>
Tylosis with oesophageal cancer  
AD†  
Carcinoma of oesophagus

Familial, juvenile, and neonatal cirrhosis  
AD† AR†  
Hepatocellular carcinoma

Hemochromatosis  
AD† AR†,6p  
Hepatocellular carcinoma

**Urogenital**  
Gonadal dysgenesis, hermaphroditism, Reifenstein's syndrome, testicular feminization  
AR† AR XR†  
Gonadoblastoma, dysgerminoma

Wilms' tumour  
AD†; 11p13, 11p15

Nephroblastomatosis  
(Perlman syndrome)

**Vascular**  
Multiple glomus tumours  
AD†

Hereditary haemorrhagic telangiectasia of Rendu-Osler-Weber  
AD†  
Angioma

Lymphedema with distichiasis  
AD†  
Lymphangiosarcoma of edematous limb

**Skeletal**  
Multiple exostosis  
AD†  
Osteosarcoma, chondrosarcoma

Cherubism  
AD†  
Fibrous dysplasia of jaws, giant cell tumour

Fibro-osseous dysplasia  
AD  
Osteosarcoma, medullary fibrosarcoma

Paget's disease of bone  
AD  
Osteosarcoma

Enchondromatosis  
AD  
Bone tumours, haemangioma (Maffucci's syndrome)

OSLAM syndrome  
AD  
Osteosarcoma

**Lymphatic and Haematopoietic**  
Histiocytic reticulosis generalized or neural only  
(Letterer-Siwe disease)  
AR† AR XR†

Familial lipochrome histiocytosis  
AR†
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Inheritance</th>
<th>Disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked hyperproliferative syndrome of Purtilo</td>
<td>XR†</td>
<td>Burkitt and other lymphomas</td>
</tr>
<tr>
<td>Kostmann infantile agranulocytosis</td>
<td>AR†</td>
<td>Acute monocytic leukemia (chromosomal breaks)</td>
</tr>
<tr>
<td>Polycythemia rubra vera</td>
<td>AR</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>Glutathione reductase deficiency</td>
<td>AR†</td>
<td>Leukemia (chromosomal breaks)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Other lymphoproliferative disorders</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Familial eosinophilia</td>
<td>AD†</td>
<td></td>
</tr>
<tr>
<td><strong>Immunodeficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bruton agammaglobulinemia</td>
<td>XR†</td>
<td>Leukemia, lymphoreticular</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>XR†</td>
<td>Lymphoreticular</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>AR† 11q 22</td>
<td>Lymphoreticular, leukemia, carcinoma of stomach, brain tumours (chromosomal breaks)</td>
</tr>
<tr>
<td>Chediak-Higashi syndrome</td>
<td>AR†</td>
<td>Pseudolymphoma</td>
</tr>
<tr>
<td><strong>Multiple System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloom's syndrome</td>
<td>AR†</td>
<td>Leukemia, intestinal cancer (chromosomal breaks)</td>
</tr>
<tr>
<td>Fanconi's pancytopenia</td>
<td>AR† 20q</td>
<td>Acute monomyelogenous leukemia, squamous cell carcinoma of mucocutaneous junctions, hepatid carcinoma and adenoma (chromosomal breaks)</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>XR†</td>
<td>Leukoplakia with squamous cell carcinoma, including of cervix</td>
</tr>
<tr>
<td>Zinsser-Cole-Engman's syndrome</td>
<td>AD</td>
<td></td>
</tr>
<tr>
<td>Nijmegen (seemanova) syndrome</td>
<td>AR</td>
<td>Lymphoreticular malignancy (chromosomal breaks)</td>
</tr>
<tr>
<td>Beckwith-Wiedemann's syndrome</td>
<td>AR† 11 p15</td>
<td>Visceromegaly, cytomegaly, macroglossia, adrenocortical neoplasia, Wilms' tumour, hepatoma</td>
</tr>
<tr>
<td>Disorder</td>
<td>Mode of Inheritance</td>
<td>Condition</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rothmund-Thomson's syndrome</td>
<td>AR†</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Werner's syndrome</td>
<td>AR†</td>
<td>Sarcoma</td>
</tr>
<tr>
<td>Osteopoikilosis</td>
<td>AD†</td>
<td>Nevi</td>
</tr>
<tr>
<td>Noonan's syndrome</td>
<td>AD†</td>
<td>Schwannoma</td>
</tr>
<tr>
<td>Focal dermal hypoplasia (Goltz's syndrome)</td>
<td>XD†</td>
<td>Mucocutaneous papillomas</td>
</tr>
<tr>
<td>Li-Fraumeni (SBLA) cancer family syndrome</td>
<td>AD†; 17p</td>
<td>Sarcomas of bone and soft tissue; young age breast carcinoma, brain tumours, leukemia, lung, and laryngeal cancer; adrenal cortical neoplasia</td>
</tr>
</tbody>
</table>

**Inborn Errors of Metabolism**

Angiokeratoma diffusa (Fabry's syndrome)                                | XR†                 |

Tyrosinemia, hypermethioninemia, galactosemia, Wilson's disease, glycogen storage disease IV | AR† AR | Posteirrhotic hepatoma |

Alpha-1-antitrypsin deficiency                                           | Codominant; 14q 31 | Hepatoma, hepatocellular carcinoma |

Vitamin D-resistant rickets                                              | XR†                 | Parathyroid adenoma |

*AD = autosomal dominant; AR = autosomal recessive; XD = X-linked dominant; XR = X-linked recessive.
† Mode of inheritance considered proved.

Mulvihill (1993) considered such genetic factors in three groups.
1. Chromosomal: entire lengths of genetic material are translocated, absent or present in excess either in every body cell (constitutional) or just in malignant tissue (Table 2-3).
2. Single locus: disease arises from a mutation in either one allelic member as a dominant trait or, in a double dose, as in a recessive trait.
3. Polygenic or multifactorial: many genes interact, perhaps with environmental factors, to cause disease, with no one factor or gene playing a predominant role. Examples of ecogenetics in childhood cancer are few as shown in Table 2-4.
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Abnormality</th>
<th>Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Trisomy</td>
<td>Preleukaemia</td>
</tr>
<tr>
<td>11</td>
<td>Deletion q13</td>
<td>Miller's syndrome of sporadic aniridia with and without Wilms' tumour</td>
</tr>
<tr>
<td>13</td>
<td>Deletion q14</td>
<td>Sporadic retinoblastoma with and without birth defects; osteosarcoma; early radiogenic sarcomas; pinealoblastoma</td>
</tr>
<tr>
<td>21</td>
<td>Trisomy</td>
<td>Acute leukaemia in Down Syndrome</td>
</tr>
<tr>
<td>X</td>
<td>Monosomy</td>
<td>Endometrial adenosquamous carcinoma in estrogen treated Turner's syndrome; possibly neural tumours</td>
</tr>
<tr>
<td>X</td>
<td>Extra</td>
<td>Breast carcinoma; extragonadal germ cell tumours in Klinefelter's syndrome</td>
</tr>
<tr>
<td>Y</td>
<td>Present</td>
<td>Gonadoblastoma in gonadal dysgenesis syndromes</td>
</tr>
</tbody>
</table>
**Table 2-4** Genetic-environmental interactions (ecogenetics) in tumours of the young (Source: Mulvihill 1993)

<table>
<thead>
<tr>
<th>Environmental Agent</th>
<th>Genetic Trait</th>
<th>Tumour or Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionizing radiation</td>
<td>Ataxia-telangiectasia with lymphoma</td>
<td>Radiation toxicity</td>
</tr>
<tr>
<td></td>
<td>Retinoblastoma</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Neviod basal cell carcinoma syndrome</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Xeroderma pigmentosum</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Ultraviolet radiation</td>
<td>Cutaneous albinism</td>
<td>Skin cancer, melanoma</td>
</tr>
<tr>
<td></td>
<td>Hereditary dysplastic nevus syndrome</td>
<td>Skin cancer</td>
</tr>
<tr>
<td>Stilbestrol</td>
<td>Turner syndrome</td>
<td>Adenosquamous endometrial carcinoma</td>
</tr>
<tr>
<td>Androgen</td>
<td>Fanconi pancytopenia</td>
<td>Hepatoma, benign and malignant</td>
</tr>
<tr>
<td>Iron</td>
<td>Hemochromatosis</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Tyrosinemia</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Monosaccharides</td>
<td>Glycogen storage disease type 1</td>
<td>Hepatic adenoma</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Purtilo X-linked lymphoproliferative syndrome</td>
<td>Burkitt and other lymphomas</td>
</tr>
<tr>
<td>Papillomavirus type 5 verruciformis</td>
<td>Epidermodysplasia</td>
<td>Skin cancer</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Virus integration site</td>
<td>Hepatocellular carcinoma</td>
</tr>
</tbody>
</table>
2.1.5 Common Childhood Cancer
Childhood cancers are generally classified according to primary organ site or cell type of the tumour. Although Miller (1969), described more than 50 forms of childhood cancers, only seven forms are most common and account for approximately 90 per cent of cases in the United States (Li 1982).

2.1.5.1 Leukaemias
Definition
The leukaemias are malignant neoplasms of the haematopoietic stem cells characterised by diffuse replacement of the bone marrow by neoplastic cells. In most cases, the leukaemic cells spill over into the blood, where they may be seen in large numbers. These cells may also infiltrate the liver, spleen, lymph nodes and other tissues throughout the body. Although the presence of excessive numbers of abnormal cells in the peripheral blood is the most dramatic manifestation of leukaemia, it should be remembered that the leukaemias are primary disorders of the bone marrow. Indeed, some patients with a diffusely infiltrated bone marrow may present with leukopenia rather than leukocytosis (Kumar et al 1992 p 365). The accumulation of an increasing number of cancerous cells in the bone marrow, leaving no room for normal blood cell production, results in a decrease in the number of normal cells in the blood. This eventually threatens the patient’s life.

Incidence
Leukaemias are the commonest form of childhood cancer. They account for about one third of new cases of cancer diagnosed each year (Behrman 1992). Leukaemias are more common in males, and peak incidence occurs between two and four years of age, although it may recur at any age. The age peak is formed by acute lymphoblastic leukaemia(ALL) which accounts for about 80% of childhood leukaemias (Li 1982). Acute nonlymphocytic leukaemia accounts for another 20% with incidence increasing with age into late adulthood. Chronic myelogenous leukaemia and other leukaemias, difficult to classify, account for the remainder. Chronic lymphocytic leukaemia is essentially never seen in children (Behrman 1992).
Acute Lymphoblastic Leukaemia

ALL is the most common type of leukaemia in childhood with an annual incidence of 3.5 per 100,000 children under 15 years of age. The highest incidence of ALL (6.9 cases per 100,000 children) is found in patients between one and five years of age (median age 4.9 years for both sexes). There is a slightly higher incidence in males than in females (ratio 1.2 to 1.0). The incidence of ALL by race and sex varies considerably throughout the world (Riehm et al 1992).

The ultimate cause of leukaemia is still unknown, but environmental agents including irradiation, chemical carcinogens and retrovirus infections have been implicated. The incidence of ALL is also higher in patients with ataxia telangiectasia (Louis-Bar syndrome), immunodeficiency and structural chromosomal abnormalities, such as Down's syndrome, Fanconi's anaemia and Bloom's syndrome (Behrman 1992, Riehm et al 1992).

The prognosis for patients with ALL has improved greatly in recent years, particularly since the introduction of prophylactic treatment of the central nervous system in the early 1970s to prevent cerebral recurrence. Approximately 50-75% of all patients today will have an unmaintained remission lasting more than 5 years and certainly the vast majority will eventually be cured (Riehm et al 1992). Behrman 1992, mentioned that the prognosis for these patients depends on the subtypes of ALL and the age of onset. Patients with onset at age less than 2 years or more than 10 years of age, with a white cell count over 100,000/mm³, or with a mediastinal mass, have unfavourable prognostic features.

Acute Nonlymphocytic Leukaemia

Acute nonlymphocytic leukaemia (ANLL) accounts for about 20% of cases of leukaemia in children. It is more common in older children and occurs with equal frequency in boys and girls. ANLL characteristically occurs in children having predisposing conditions such as Fanconi anaemia and Bloom's syndrome, in which there is excessive chromosomal breakage or as a second tumour after cancer chemotherapy (Behrman 1992).
The prognosis of patients with ANLL is worse than the lymphoid group; 30-40% of patients can be expected to be cured with chemotherapy alone (Behrman 1992) and up to 60% with bone marrow transplantation (Hall 1994).

**Chronic Leukaemia**

Chronic granulocytic leukaemia is the most common proliferative disease in children, accounting for approximately 2-5% of cases of childhood leukaemia. Two main types of well-differentiated myelocytic leukaemia have been recognised. One is clinically and haematologically comparable with the adult form of chronic myelocytic leukaemia and appears in children above the age of four years. The other presents earlier in infancy, with granulocytic and monocytic proliferation, and clinically pursues a much more rapid course with an increased incidence of haemorrhage and infection (Schaison et al 1992).

Adult type chronic myelocytic leukaemia is a clonal panmyelopathy involving all the haematopoietic cell lineages and at least some of the lymphoid cells. There is a specific cytogenetic marker, the Philadelphia (Ph') chromosome, a translocation (9;22) (q34;q11).

The adult type of chronic myelocytic leukaemia accounts for only 3% of cases of leukaemia in children. The age of maximal incidence in children is 10-12 years. The condition has been seen with increased frequency in individuals exposed to radiation from the atomic bombs (Behrman 1992).
2.1.5.2 Malignant lymphomas

Definition
Lymphomas are malignant neoplasms of cells native to lymphoid tissue (i.e., lymphocyte and histiocytes and their precursors and derivatives). The term lymphoma is somewhat of a misnomer because all these disorders are malignant and, unless controlled by therapy, ultimately lethal.

Two broad groups of lymphoma are recognised: Hodgkin's disease (Hodgkin's lymphoma) and non-Hodgkin's lymphoma (NHL). Although both arise in the lymphoid tissue, Hodgkin's disease is set apart by the presence in the lesions of the distinctive Reed-Sternberg giant cells and by the fact that in the involved nodes non-neoplastic inflammatory cells frequently outnumber the neoplastic element represented by the Reed-Sternberg cell (Kumar et al 1992 p 354).

Incidence
Lymphoma is the third most common malignant disease in children after leukaemia and CNS tumour. Frequencies vary widely among different countries; the highest being found in the Middle East, Nigeria and Uganda. Lymphomas represent about 10% of all malignant diseases in childhood, with a slight predominance of non-Hodgkin's lymphoma (NHL) over Hodgkin's disease (Young et al 1986).
2.1.5.3 Hodgkin's disease

Definition
Hodgkin's disease rarely occurs before the age of five years. The incidence increases steadily thereafter to a peak at 15 - 34 years of age and a second peak after the age of 50 years. The condition is almost twice as common in boys as in girls. No definite causal factors are known, but occurrence in like-sex siblings has suggested a virus of low virulence and infectivity. Hodgkin's disease appears to arise in T-dependent areas of lymphoid tissue. The central histologic feature is the Reed-Sternberg cell. It is thought to originate from an antigen-presenting cell of the mononuclear phagocyte- reticulum cell lineage, perhaps from the interdigitating reticulum cell. There is increasing evidence that Epstein-Barr virus may be involved in the pathogenesis (Behrman 1992).

Prognosis
With current treatment, more than 90% of patients with Hodgkin's disease achieve a complete initial clinical remission. The likelihood of prolonged remission or cure is related primarily to the stage at diagnosis. Most patients with involvement of a single lymph node region, or of a single extra-lymphatic organ or site (Stage I), and involvement of lymphoid regions on the same side of the diaphragm (Stage II), will be cured. Approximately 75% of those in Stage III (involvement of lymph node regions on both sides of the diaphragm) will be cured with both chemotherapy and radiation. At least 50% of those in Stage IV (diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues) can be cured with intensive chemotherapy (Behrman 1992).
2.1.5.4 Non-Hodgkin's lymphoma

Definition

Non-Hodgkin's lymphoma (NHL), a heterogenous group of solid lymphoid tumours, is more common than Hodgkin's disease in young children. It affects boys about three times as frequently as it does girls. Both congenital and acquired immunodeficiencies, including acquired immunodeficiency syndrome (AIDS), predispose to the development of this type of lymphoma. Children with infantile X-linked agammaglobulinemia or severe combined immunodeficiency have about a 5% incidence of malignancy, usually lymphoma and children with Wiskott-Aldrich syndrome and ataxia-telangiectasia a 10% or greater incidence. The incidence of lymphomas is increased also in immunosuppressed patients after renal transplantation (Behrman 1992).

A form of lymphoma in American patients resembles the Burkitt lymphoma of African children. Burkitt's lymphomas, monoclonal proliferation of malignant B lymphocytes, are characterised by one of three cytogenetic abnormalities: t (8;14)(q24:1;q32.3), t(2;8)(p12;q24) or t(8;22)(q24;q11). Of particular interest is the localisation of immunoglobulin genes to the segments involved in the translocation. In epidemiologic studies, Burkitt's lymphoma in Africa has been shown to be causally related to Epstein-Barr virus infection in children under the age of 15 years. The American lymphoma, however, does not have a nearly universal association with Epstein-Barr virus (Behrman 1992). There is evidence that the development and onset of African Burkitt's lymphoma results from the host's response to prolonged, severe malarial infection (Robison et al 1991).

Prognosis

The complete initial clinical remission of patients with non-Hodgkin's lymphoma is related to the stage at diagnosis. A system devised for non-Hodgkin lymphoma in childhood is shown in Table 2-5. With current treatment, perhaps 90% of patients with stage I and II disease can expect to be cured, as can about 50% of those with stage III and IV disease. Once the tumour has spread to the bone marrow and undergone "leukaemic conversion" the prognosis is worse (Behrman 1992).
Table 2-5  A staging system for non-Hodgkin lymphoma in childhood
(Source: Behrman 1992)

Stage I
A single tumour (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen.

State II
A single tumour (extranodal) with regional node involvement.
Two or more nodal areas on the same side of the diaphragm.
Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm.
A primary gastrointestinal tract tumour, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, which must be grossly (>90%) resected.

Stage III
Two single tumours (extranodal) on opposite sides of the diaphragm.
Two or more nodal areas above and below the diaphragm.
Any primary intrathoracic tumour (mediastinal, pleural, thymic).
Any extensive primary intra-abdominal disease.

Stage IV
Any of the above, with initial involvement of CNS and/or bone marrow at time of diagnosis.
2.1.5.5 Tumours of the central nervous system

Definition
Central nervous system tumours arise from central nervous system (CNS) parenchymal cells. Each type of cell in this system gives rise to its own particular type or types of tumour (Kumar et al 1992 p 720). There are two major histologic types of brain tumour in children, glial cell tumours and those of primitive neuroectodermal cell origin. Glial cell tumours are the most common and consist of a variety of cell types with variable prognosis including the astrocytoma, ependymoma and glioblastoma multiforme. Neuroectodermal tumours probably arise from a primitive, undifferentiated cell line and are prominent throughout the CNS, involving the cerebellum (medulloblastoma), cerebrum, pineal gland (pineoblastoma) and spinal cord (Behrman 1992). Generally, infratentorial tumours, located in the posterior fossa, are more prevalent in the paediatric age group. In contrast, in infants less than 2 years of age, and adolescents, the frequency of supratentorial tumours is equivalent to those located in the posterior fossa. Approximately two thirds of all intracranial tumours between the ages of two and twelve are infratentorial in location. Supratentorial tumours predominate in the adult (Behrman 1992).

Incidence
Tumours of the CNS are the most common type of solid tumour and second only to leukaemia as the most prevalent malignancy in children aged under 14 years (Tait et al 1992). The most common CNS neoplasms in childhood are astrocytoma, glioblastoma, medulloblastoma and ependymoma (McWhirter and Masel 1987 p 125, Robison et al 1991). Before puberty the risk of CNS tumour is slightly higher for boys; after puberty, it is greater for girls (Gold and Gordis 1979).

Despite unknown aetiology of the CNS tumour, the recognition of predisposing familial characteristics provides a focus for possible genetic abnormalities underlying them. Increased rates of leukaemia and of other brain tumours have been noted among relatives of children with primary CNS tumours. Additionally an association with epilepsy has been demonstrated in siblings of children who have CNS tumours. CNS tumours occur
with increased frequency in children who have other underlying diseases, including neurofibromatosis, tuberous sclerosis and primary immunodeficiencies (Robison et al 1991).

2.1.5.6 Neuroblastoma

Definition

Neuroblastoma, or sympathicoblastoma, is a highly malignant neoplasm arising from embryonic sympathetic neuroblasts or occasionally from other neural crest remnants. It, therefore, locates at the same anatomical location of the sympathetic system. By virtue of its origin, a neuroblastoma has the potential to mature into either ganglioneuroma or phaeochromacytoma (Voûte et al 1992). More often than other tumours, neuroblastoma is capable of undergoing spontaneous regression, usually in infants under the age of 6 months (McWhirter and Masel 1987 p 9). Most neuroblastomas originate in the adrenal gland or retroperitoneal sympathetic ganglia. Although primary neck tumours arising from cervical sympathetic ganglia have been reported, they are rare and represent less than 5% of all neuroblastomas (Batsakis 1979).

Incidence

Neuroblastomas are almost exclusively childhood malignancies. They are the commonest type of malignancy in children under the age of 1 year and over 80% occur in children under 6 years of age (de Lorimier 1969, McWhirter and Masel 1987 p 9, Voûte et al 1992). The tumours are exceeding rare after the age of 16 years. They are surpassed in frequency only by leukaemia and central nervous system tumour. They are the second most common solid tumour, accounting for approximately 5% of all childhood malignancies (de Lorimier 1969).

The aetiology is unknown but familial cases occur. There is also an association with neurofibromatosis, Hirschsprung's disease, heterochromia, foetal hydantoin and foetal alcohol syndrome, and Friedreich's ataxia. Rearrangement or deletion of the short arm of chromosome 1 has been found in 80% of cases (Sinniah and Evans 1992).
Prognosis
The success of treatment in neuroblastoma depends greatly on age and stage. The older the patient and the more widespread the disease, the worse will be the prognosis. Patients whose tumours can be completely resected may do well. Local irradiation may be used if there are small amounts of residual tumour. Patients with bilateral extension of midline disease and with remote disease involving skeleton, organs, soft tissue, distant nodes and so on, generally receive chemotherapy. Patients under one year of age may tolerate chemotherapy less well, but are more likely than older patients to have a successful response to chemotherapy (Behrman 1992).

2.1.5.7 Retinoblastoma
Definition
Retinoblastoma is a primary malignant intraocular neoplasm, arising in the retinal cell. It is the paradigm of genetic susceptibility to human cancer. It is caused by the loss in a developing retinal cell of both of a pair of tumour-suppressing genes or "anti-oncogenes", one of which is situated on the long arm of each chromosome 13 (Hungerford et al 1992). Studies of the epidemiology of retinoblastoma led Knudson to his seminal "two-hit" models of carcinogenesis (Sinniah and Meadows 1992).

Incidence
Retinoblastoma is the most common malignant intraocular tumour in children. It has two forms: hereditary (40%) and non-hereditary (60%). The heritable forms of retinoblastoma have characteristic clinical features, such as an early age at onset, tendency to bilateral involvement and second primary tumour, predominantly sarcomas (Robison et al 1991). About one-third of all cases are bilateral and such cases are caused by an autosomal dominant gene. They are usually diagnosed during the first year of life and are rare after the age of five years (Hungerford et al 1992).

The sporadic or non-heritable form of retinoblastoma usually has unilateral involvement and are diagnosed during the second or third years of life. Environmental factors have been speculated to be important in this form of retinoblastoma, but very few analytical
studies have been undertaken. Although several factors, including prenatal exposure to X-ray, morning sickness medication and decreased exposure to prenatal vitamins (first trimester), barrier contraception and spermicidal jelly have been reported, additional studies will be needed to reproduce and elaborate on these potential environmental factors (Robison et al 1991).

**Prognosis**

The survival rate of the primary retinoblastoma with intraglobal extension is between 85-100%. Less than 10% of patients have extraglobal extension of the disease at the time of presentation. No cures have been reported in patients who have had massive orbital disease or extensive optic nerve involvement when first seen, because intracranial spread and distant metastases have already occurred. If microscopic examination finds a tumour in the periglobal tissues of the optic nerve, there is about a 30% chance of long-term survival with irradiation and chemotherapy. Recent studies have indicated that overall survival of these patients in the third and fourth decade of life may be considerably lower because of their high incidence of second malignancies (Behrman 1992).

### 2.1.5.8 Wilms' tumour

**Definition**

Wilms' tumour, also known as renal embryoma or nephroblastoma, is the most common of the primary malignant renal lesions of childhood (D'Angio 1992a). It is third most common organ cancer in children under the age of 10 years. It is therefore one of the major solid cancers of children. These tumours contain a variety of cell and tissue components, all derived from the mesoderm (Kumar et al 1992 p 469).

Wilms' tumour, like retinoblastoma, may arise sporadically or be familial with the susceptibility to tumourigenesis inherited as an autosomal dominant trait. Many tumours are associated with deletion in the short arm of chromosome 11 (11p13) and loss of cancer suppressor gene WT-1. Recent studies suggested that, unlike childhood retinoblastoma, Wilms' tumour is genetically heterogenous and in some cases loci other than 11p13 are involved (Kumar et al 1992 p 469). The familial form of Wilms' tumour
is more likely to be bilateral than the sporadic form. Moreover, patients with bilateral or familial disease also have a higher incidence of congenital anomalies, and their tumour may develop at an earlier age. It is estimated that a child of a patient with bilateral or familial Wilms' tumour has a 30% risk of developing the tumour (Behrman 1992).

Incidence
Wilms' tumour has a maximum incidence at the age of 1-5 years. It can occur in the newborn or the young baby but is rare after the age of 8 years (Tournade et al 1992). It occurs with approximately equal frequency in both sexes and in all races (Behrman 1992).

An important feature of Wilms' tumour is its association with congenital anomalies. The most common association is with genitourinary anomalies, hemihypertrophy, sporadic aniridia, Beckwith-Wiedemann syndrome or renal ectopia (McWhirter and Masel 1987 p 9, Behrman 1992).

Prognosis
In general prognosis is better in children diagnosed before the age of 2 years and with a Wilms' tumour weighing less than 250 grams. The most significant prognostic variables, however, are histology and age. Any recurrence of the disease carries a poor prognosis (Behrman 1992).

2.1.5.9 Rhabdomyosarcoma

Definition
Rhabdomyosarcoma is a tumour that may arise from the same embryonic mesenchyme as striated skeletal muscle. It can occur anywhere in the body where striated muscle is found (Behrman 1992).

Incidence
Rhabdomyosarcoma is the commonest soft tissue cancer of childhood. It accounts for more than half of soft tissue sarcomas and for 5% of all childhood malignancies. The incidence of rhabdomyosarcoma appears to be a bimodal curve. An early peak occurs before 5 years of age, with common tumours of neck, head, prostate, bladder and vagina.
A later peak occurs around 15-19 years of age, with involvement of the genitourinary tract (particularly of the testes or paratesticular tissue). There is a slight predominance of male patients (Behrman 1992).

There appears to be a familial aggregation of rhabdomyosarcoma with other sarcoma. Rhabdomyosarcoma may complicate neurofibromatosis. In addition, patients with rhabdomyosarcoma are often found in "cancer families" with Li-Fraumeni syndrome, in which there is a high incidence of brain tumour and breast cancer at an early age, particularly in parents (Behrman 1992).

Prognosis
Broadly, rhabdomyosarcomas can be divided into three groups: those with good, fair and poor prognosis. The good prognosis group generally has embryonal histology and localised disease in a superficial locus, such as the orbit, cheek, paratestis, or vagina. Of these patients with resectable tumour, 80-90% have prolonged tumour-free survival. In addition, unresectable tumour localised at certain favourable sites (such as orbit) has a high likelihood of cure.

Fair prognosis patients have invasive tumours in deeper sites, such as parameningeal head sites, bladder, prostate; or limbs: they may be of embryonal or alveolar histology and often involve regional nodes. About two-thirds of patients with incompletely resected regional tumour will also achieve long-term disease-free survival.

Poor prognosis patients have distant metastases, which are most often pulmonary but may also involve distant nodes, marrow and bone. Only about half of these patients will achieve remission and less than half of them will be cured.

Older children not only have a worse prognosis than younger ones but also have a greater frequency of lesions of the extremities and of alveolar histology (Behrman 1992, Womer and Sinniah 1992).
2.1.5.10 Bone tumours

Osteosarcoma and Ewing's sarcoma are the commonest bone tumours of childhood, with a peak incidence in adolescence. Osteosarcoma, the most common malignant bone tumour, is twice as common in white children as Ewing tumour. Ewing tumour almost never occurs among black children. Rare bone tumours include chondrosarcomas and fibrosarcomas (Behrman 1992).

Osteosarcoma

Definition

Osteosarcoma has been defined as a primary malignant bone tumour, the neoplastic cells of which produce osteoid. The classic osteosarcoma arises within the medullary canal of the shaft and may break through the cortex of bone of origin to form a soft tissue mass which can achieve considerable size. The tumour may also extend along the medullary cavity. Osteosarcoma has some important subclassifications. Parosteal osteogenic sarcoma is a well-differentiated extramedullary tumour of low metastatic potential. Surgical resection alone is often adequate therapy. In contrast, a similarly located lesion, periosteal osteogenic sarcoma, is histologically a much more pleomorphic lesion that behaves more aggressively clinically. Telangiectatic osteosarcoma is a bloody, cystic lesion that produces no new bone radiographically and may be confused with an aneurysmal bone cyst. Prognosis may be poor (Behrman 1992).

Osteosarcoma can arise in any bone. It, however, occurs most commonly in long bones at the metaphyseal ends, the areas of most active growth and reconstruction. The most common primary site is the distal femur, followed by the proximal humerus and proximal tibia (Behrman 1992).

Incidence

Osteosarcoma represents half of the bone cancer seen in children 14 years of age and younger. Approximately 80% of childhood cases are diagnosed between the ages of 10 and 14 years and affected girls slightly outnumber affected boys with a ratio of 1.3:1 (Robison et al 1991).
Osteosarcoma is associated with hereditary retinoblastoma as a secondary malignancy. It has also been well-documented to be radiation associated. Certain diseases of bone, some genetically determined, may also predispose to osteosarcoma. These include multiple osteochondromatosis (Ollier disease), which may also be found with haemangiomas (Maffucci syndrome); multiple hereditary exostoses; osteogenesis imperfecta; and Paget's disease. It occurs also as a secondary tumour in the treated bone of long-term survivors of Ewing's tumour; latency period ranges from four to over 20 years (Behrman 1992).

**Prognosis**

Prognosis is best with low grade tumours such as parosteal osteosarcoma. With surgery alone about 20% of patients with the classic form of osteosarcoma will have long-term survival. The survival rate after intensive chemotherapy is not yet known but will be at least 50%. Some cases of long-term survival have followed resection of metastatic pulmonary disease, but none have occurred in patients with diffuse pulmonary metastases or metastatic disease to bone (Behrman 1992).

**Ewing's Sarcoma**

**Definition**

Ewing's sarcoma is a round-cell tumour of bone of later childhood and adolescence. The tumour cells contain glycogen, often Periodic Acid Schiff reagent (PAS)-positive, and frequently demonstrate the reciprocal chromosome translocation t(11;22) (q24;q12). This karyotypic abnormality is also present in the peripheral neuroectodermal tumour, which suggests that at least some tumours within the Ewing tumour complex are of neuroectodermal origin (Belasco 1992).

The tumour may arise either in long bones of extremities or in flat bones of the head and trunk. As with osteosarcoma, the most commonly involved long bone is the femur. The most commonly involved flat bone is the pelvis. Metastatic disease most frequently involves lungs and bone, occasionally bone marrow and central nervous system. This is present in up to one-third of patients at the time of diagnosis (Behrman 1992).
Incidence
Ewing's sarcoma is less common than osteosarcoma. It is more common in males than in females. The age specific incidence pattern for Ewing's tumour is similar to that of osteosarcoma. The most striking feature of Ewing's sarcoma is the extremely low incidence in blacks, Japanese, and Chinese. Relatively little is known about the epidemiology and aetiology of Ewing's sarcoma. Instances of familial occurrence of Ewing's sarcoma have been reported, but the evidence is not compelling enough to suggest that an inherited genetic component exists. Unlike osteosarcoma, ionising radiation does not appear to place children at increased risk of Ewing's sarcoma as a second malignancy (Robison et al 1991).

Prognosis
A poor prognosis is associated with metastatic disease at the time of diagnosis and a proximal primary site. Primary tumours in pelvis, humerus or rib carry a worse prognosis than those in distal long bones. Recent trials with combinations of drugs and irradiation indicate that 40-60% of patients who re-present without metastatic disease will be free of tumour at 3 years. Late relapses can occur (Behrman 1992).

2.1.5.11 Gonadal and germ cell neoplasms
Definition
The germ cell tumours are an interrelated group of malignancies expressing the multipotential characteristics of differentiation of cells from which they arise (Behrman 1992). During embryogenesis primordial germ cells (derived from yolk sac endoderm) migrate to the midline urogenital ridge in the retroperitoneal region and give rise to the gonads. This migration can be inexact at times and primordial germinal tissue can locate aberrantly in extragonadal sites, usually midline. When these cells or their progeny undergo malignant transformation, tumours develop in the gonadal sites for those cells that have migrated normally, or extragonadal sites for those that erred. The gonadal primary sites account for over 50% of germ cell tumours. Extragonadal tumours are found in predictable sites such as the sacrococcygeal region, anterior mediastinum, retroperitoneal region and intracranially. The widely accepted classification of germ cell
tumours, as shown in Figure 2-3, was advanced by Teilum (Baker and Bunin 1992).

Incidence

Gonadal and germ cell tumours are uncommon in children. It constitutes 3% of all childhood cancers (Baker and Bunin 1992). However, sacrococcygeal teratoma is the most common solid tumour in newborns (1:40,000 live births). Most reports indicate a female preponderance. The age incidence for both ovarian and testicular tumours peaks before the age of 2 years, with a second increase in rate beginning after the age of 6 years for ovarian tumours and after the age of 14 years for testicular tumours (Behrman 1992).

Prognosis

The prognosis of germ cell tumours depends mainly on the extent of the disease at the time of diagnosis. It is important, therefore, that germ cell tumours be suspected as early as possible. In general, the finding of extraembryonal elements in a germ cell tumour denotes a poor prognosis (Behrman 1992).

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**Figure 2-3**  Schematic relating maturation of germ cells to their malignant counterparts (Source: Baker and Bunin 1992)
2.2 CANCER THERAPY

The effective modern paediatric cancer therapy requires a close collaboration among specialists in a multidisciplinary team, including surgeon, radiotherapist, chemotherapist, pathologist, radiologist, and others. This discussion encompasses a brief introduction to the bases and the practical aspects of the three major cancer treatment modalities of surgery, radiation therapy, and chemotherapy.

2.2.1 Surgery
Historically, the first major advance in the management of childhood cancer was surgical excision of the primary malignant tumour. Even with the radical surgical procedures that became possible with improved anaesthesia and supportive care, survival was brief and cure rates were low. The addition of radiation therapy as an adjunct to the excision of the primary tumour improved survival only modestly. During the 1960s, when the importance of micrometastases was recognised, combined-modality therapy produced dramatic changes in the outlook for children with malignant disease and became the standard of care. Now approximately 60% of children are cured as compared with a meagre 20% a few decades ago (Lampkin et al 1985).

2.2.1.1 Roles of surgery
Paediatric surgery has an important role in the multidisciplinary treatment of childhood cancer. Surgery is still the best therapy to eliminate the primary tumour, and it is essential for histopathologic diagnosis and staging. Second- and third-look surgical procedures have become commonplace. Surgery is often essential in the management of metastatic disease, for the treatment of complications secondary to therapy, and for supportive care that may be required. In contrast to the traditional radical surgical approach, the modern paediatric surgery avoids mutilating procedures whenever possible (Shochat and Hartman 1991).
Diagnostic biopsy

The critical diagnostic step in any cancer is obtaining proof of malignancy. No logical treatment plan can be formulated until an accurate diagnosis is made and this often requires biopsy. Diagnostic biopsy material can be obtained by a variety of techniques, including:

- Aspiration biopsy,
- Needle biopsy,
- Incisional biopsy,
- Excisional biopsy,
- Endoscopic biopsy - in the bladder, testis, chest, etc., and

The biopsy ideally should be performed at a facility that can provide complete patient care - histologic, surgical, and adjunctive (chemotherapy and radiation therapy). The type of biopsy performed must be tailored to the lesion with consideration of several factors, including adequacy of tissue for all proposed investigations, risks, ease of access, comfort to the child, and cosmetic result (Plaschkes and Rao 1992).

Surgical staging

The staging of tumour is the delineation of its spread. A common classification of staging is the TNM system, in which the T stands for primary tumour size and local spread, the N stands for presence or absence of lymph node metastases and while the M relates to presence or absence of distant metastases. Each letter is followed by a number that correlates with size and degree of involvement (Brown et al 1992).

Staging is critical in planning proper therapy. Although advances in diagnostic radiology and nuclear medicine have facilitated the staging process, operative staging is still necessary for certain neoplasms such as Hodgkin's and non-Hodgkin's lymphomas. Accurate knowledge of the extent of the tumour enables the chemotherapist and radiotherapist to refine therapy so that minimal treatment is provided to children at
relatively low risk and more intensive therapy is reserved for those at high risk. One form of operative staging, response staging, is also important in many childhood malignancies. It is performed after chemotherapy or radiation therapy, either as a delayed primary excision or a second-look procedure. The aim of a second-look procedure is to remove the tumour completely for cure or to obtain information so that further therapy can be planned. Occasionally a third procedure may have to be done in the hope of accomplishing total excision of neoplasm (Shochat and Hartman 1991).

**Operative therapy**

The main objective of operative treatment is always the adequate rather than the radical excision of the tumour. The strategy differs depending on the size, location, stage, and nature of the tumour. There are several surgical procedures involved in this stage of treatment including (Shochat and Hartman 1991, Plaschkes and Rao 1992):

- Primary surgical excision, the most important therapy for solid tumours particularly ones arising in a paired organ (for example, eye, kidney, adrenal, ovary or testis) and not invading vital structures.

- Delayed primary excision after chemotherapy and/or radiotherapy for tumours sensitive to chemotherapy and/or radiotherapy, such as rhabdomyosarcoma, in order to minimise disfiguring procedure.

- Debulking, partial removal without curative intent in order to make subsequent therapy with drugs, radiation or adjuvant measures more effective.

- Restaging, for assessing further treatment, i.e. second-look surgery.

- Excision of metastatic disease.

- Palliative surgery to relieve pain.
Supportive procedures
Some surgical procedures are also essential for supportive care. The central venous catheterisation is a common procedure for providing an access for blood withdrawal and delivery of parenteral nutrition, antineoplastic agents, antibiotics, anticoagulants, and other solutions. These catheters are placed by direct exposure in the cephalic, external or internal jugular, or saphenous systems, or they have been placed percutaneously through the subclavian vein. Other supportive procedures may include numerous surgical interventions to prevent or treat several complications which can arise from any form of cancer treatment (Hays and Atkinson 1993).

2.2.2 Radiation Therapy
The use of radiation to treat cancer was first reported within a year of Röentgen's discovery of x-rays in 1895. The initial "caustic" applications of this new modality evolved over the next 30 years to various courses of irradiation capable of killing tumour cells while sparing adjacent normal structure (del Regato et al 1985).

2.2.2.1 Roles of radiation therapy
Radiotherapy has two major roles in cancer treatment: curative and palliative. Radiotherapy is curative when given in conjunction if a localised, primary tumour has been biopsied or incompletely removed.

Curative radiotherapy is adjunctive if it is applied to primary tumours or sites of potential spread when malignant cell burden is microscopic, or below the level detectable by current imaging methods.

Palliative radiotherapy is indicated when tumours become uncontrollable. Relatively short courses of radiation are delivered to the troublesome part for several purposes, including reduction of pain, relief of compression and obstruction, reduction of cosmetically disfiguring mass, and control of haemorrhage (Mandell and Wharam 1991).
2.2.2.2 Nature of ionising radiation

Ionising radiation is radiation that, during absorption, causes the ejection of an orbital electron. This leaves free radicals that cause chemical changes due to the breakage of the chemical bonds and thus produces biologic effects (Tarbell and Weichselbaum 1986). Ionising radiations encompass several types.

Photons

Photons are bundles of pure energy in motion through space. They lack both mass and charge, and have an undulant (wave) path (D'Angio 1992b). The examples of photons are x-ray and gamma rays. X-rays result from the conversion of electrical energy into a beam of x-rays when electrically accelerated electrons are stopped rapidly. Gamma(γ) rays are emitted spontaneously by the nuclei of radioactive elements, such as cobalt-60, during the process of nuclear decay (Kun and Moulder 1993).

Atomic particles

Accelerated bits of the atom can also be ionising. Particulate radiations ionise directly by electron ejection and indirectly by absorption within the atomic nuclei, leading to nuclear disruption with the resultant emission of nuclear particles and ultimately ejecting orbital electrons (Kun and Moulder 1993). Atomic particles have mass and weight. They can be charged particles such as electrons with a single negative charge and protons or helium nuclei with positive charges. Neutrons, which are 'heavy' particles without charge, are also another example (D'Angio 1992b).

Ionising radiation can also be categorised according to the energy of the machine: superficial, orthovoltage and supervoltage radiation.

Superficial radiation defines the radiation energies between 50 and 140 keV (keV=100 electron volts).

Orthovoltage radiation is designated between 140 and 500 keV.

Orthovoltage and superficial machines yield an advantage in the treatment of skin or other superficial tumours because the maximum dose falls off rapidly below the surface.

Supervoltage radiation refers to radiation energies of greater than 500 keV. Clinically important advantages are seen when radiation reaches 500 keV because, above this
energy, there is reduced absorption in bone, less damage to skin at portal entry, and reduced scatter of radiation into other tissues. Supervoltage radiation is also of great importance in treating tumours deep in the body because the maximum dose occurs below the skin. The percent of radiation at any specific depth, compared with the maximal dose, increases as the energy increases and produces a therapeutic advantage (Tarbell and Weichselbaum 1986).

2.2.2.3 Forms of ionising radiation

There are two major forms of radiation therapy: teletherapy and brachytherapy. 

Teletherapy, 'tele' from the Greek for 'distant', indicates ionising radiation therapy emanating from a distant source. Examples are x-ray machines, linear accelerators, and cobalt-60 teletherapy apparatus. The beam is confined through mechanical means, and can further be defined by the use of accurately shaped, individually made heavy metal blocks or shields. Teletherapy is used when a deep-seated tumour must be treated. The techniques used (for example, multiple fields) deliver higher doses at depth relative to those received by skin.

Brachytherapy, 'brach' from the Greek root for 'short', involves the use of ionising radiations placed close to the tissue to be irradiated. This can be done through the placement of needles within the tumour itself, the insertion of encapsulated sources within hollow cavities such as the uterus or maxillary sinus, or the use of applicators placed directly on the surface such as for skin carcinoma. The advantage is that the dose is high within the volume to be irradiated and falls off rapidly with distance, so that surrounding normal tissues receive a small fraction of the calculated tumour dose (D'Angio 1992b).

2.2.2.4 Biological effects of ionising radiation

It is the high-energy orbital electrons that cause biologic injury by damaging the cell's nuclear deoxyribonucleic acid (DNA). Although these fast electrons may interact directly with DNA to cause disruption in its structure, it is more likely that the injury is mediated
by an indirect mechanism involving water molecules, which make up about 80% of the cell. The ejection of an electron from a water molecule leaves a charged molecule that has an unpaired electron in its outer shell. This free radical is a highly reactive chemical species of short duration that decays to form an uncharged free radical by interacting with another water molecule as follows:

\[ \text{H}_2\text{O}^+ + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{OH}^- \]

The hydroxyl radical, OH, is uncharged, has a longer life than an ion radical, and can travel about 10 Å. The chemical bonds of DNA are easily disrupted by interaction with hydroxyl radicals. Chromosome breaks result, some of which may be repaired. If not repaired, the aberrant chromosomes may prevent subsequent mitosis or be retained as mutations. Tumour cells may undergo more than one mitosis before they are no longer clonogenic (Mandell and Wharam 1991).

The purpose of the radiation is to destroy the reproductive capacity of the cell. Usually, radiation does not lead to direct cellular death, although it can do so in exquisitely sensitive cells such as lymphocytes. Rather, the effect of the radiation is to reduce the capacity of the cell to produce viable progeny which leads to cell death. Impaired mitosis after radiation is a dose-related phenomenon. The more radiation is given, the more cells are damaged. Although there are no consistent differences between radiation survival curves for cells of normal and tumour origin, there is evidence that variation in cellular sensitivity is one of the factors affecting tumour radiosensitivity (Kun and Moulder 1993).

The cellular susceptibility to lethal radiation injury varies upon its phase in the cell cycle (Figure 2-4). Despite variation among cell lines, the study using synchronised population of cells revealed some generalisations of the effects of radiation at different stages in the cell cycle as follows (Sinclair and Morton 1966, Sinclair 1968):

1. Cells are generally more sensitive near or at mitosis.
2. If G1 is appreciable in length, a resistant period is evidenced early, followed by a decline in survival toward S; the end of G1 may be as sensitive as M.
3. In most cell lines, resistance rises during S to a maximum in the later part of S, and this is usually the most resistant part of the cycle.
4. In most cell lines, G₂ is as sensitive as M.

Figure 2-4  Diagrammatic representation of the cell cycle
Cells in cycle are in G₁, S, G₂ or M phase; cells not in cycle are either resting in G₀ or proceeding to differentiate and eventually to die.
(Source: Weiden 1986)

In general, the more 'immature' the cell and the more rapidly dividing it is, the more radioresponsive it is likely to be. This affects not only neoplastic cells, but also many normal cells within the body (for example, bone-marrow stem cells, intestinal crypt cells, basal cells of epidermis) which divide regularly. In children, virtually every tissue is dividing rapidly therefore more underlying tissues can be damaged compared with adults (D'Angio 1992b). The acute radiation tolerance of rapidly proliferating tissues is relatively low. These tissues response to radiation within days or weeks. Cells that do not divide (for example, mature muscle and nerve cells) are radioresistant, showing little or no decrease in numbers after radiation. The slowly dividing cells also have relatively higher acute radiation tolerance and their responses may be months or years after irradiation (Kun and Moulder 1993).
The goal of therapeutic irradiation is to achieve a favourable therapeutic ratio by causing the death of all tumour cells that are capable of indefinite division without producing unacceptable damage to adjacent normal tissues. The favourable therapeutic ratio is based on the differential effect between normal and tumour cells. Several factors should be manipulated to improve the therapeutic ratio.

### 2.2.2.5 Factors influencing the radiation effect on tumour

#### Tumour types
From clinical observation, it is apparent that certain paediatric tumours regress more rapidly than others following radiotherapy and are less likely to recur after standard doses. The more radiosensitive group includes germinoma, lymphoma, Hodgkin's disease, leukaemia, Wilms' tumour, and neuroblastoma. Bone and most soft tissue sarcomas and brain tumours are relatively resistant (Mandell and Wharam 1991).

#### State of oxygenation
The reduction of oxygen tensions below those normally present in tissue leads to a substantial reduction in cell killing. Hypoxic tissue requires 2.5 to 3 times the radiation dose to achieve the same degree of cell death seen in normally oxygenated tissues. Also it is well known that the centre of tumours is necrotic and may consist of a significant number of hypoxic cells. This may unfavourably alter the therapeutic ratio. Several measures have been used to reduce the relative resistance of these cells. These include the use of particle radiation with neutron and pi-mesons, reoxygenation of tumours with hyperbaric oxygen, and the use of radiation sensitisers such as misonidazole and etanidazole (Kun and Moulder 1993).

#### Recovery capacity
Because of biochemical abnormalities including deficiencies of enzymes needed for DNA repair, tumour repair is less effective. It is thus possible to eradicate the tumour without irreparable damage to the patient. However, this differential recovery between normal and abnormal cells after damage may be very small (Barrett and Donaldson 1992).
2.2.2.6 Techniques minimising radiation damage to normal tissue

Use other effective therapy

Radiation therapy can be avoided if there are similar or more effective modes of treatments available. This has been made more possible through the advent of effective chemotherapeutic agents. Systemically administered drugs can, in a sense, substitute for radiation therapy. That is, not only can systemic chemotherapy suppress micrometastases in distant sites, but it can also contribute to the original site; for example, after incomplete surgical excision of a tumour where microscopic nests of neoplastic cells may remain. This is, however, a double-edged sword. Certain chemotherapeutic agents can enhance and 'reactivate' latent radiation damage in tissues; for example, dactinomycin and doxorubicin (Adriamycin) can augment radiation side-effects, converting tolerable doses to levels that may cause severe tissue damage (D'Angio 1992b).

Radiation fractionation

Fractionated radiotherapy refers to a strategy of dividing a course of treatment into a series of smaller doses. The aims of the technique are to allow recovery of normal cells and to reduce the severity of 'late effects' (Barrett and Donaldson 1992).

The technique commonly used in paediatric oncology is the conventionally fractionated radiotherapy of single daily doses of 100-200 cGy, 5 days per week, until the planned total dose has been given. The total duration of treatment is often between 2 and 6 weeks (McWhirter and Masel 1987 p 51).

Radioprotectors

These include the introduction of heavy metal blocks in the beam to protect sensitive structures that do not need to be included in the treatment volume. Examples are shields for lens of the eye when tumours in nearby structures must be treated. These blocks can be extremely elaborate, not only having complex shapes, but also being introduced into moving beams so that the part to be protected is, in effect, placed in 'eclipse' as the treatment machine rotates around the patient (D'Angio 1992b).
Chemical compounds that protect normal tissue more effectively than tumour from radiation injury permit delivery of higher total radiation doses without an increase in normal tissue damage. The most effective radioprotectors are the sulphydryl compounds, which act by scavenging free radicals and restoring free radical damage.

Prominent among the thiol compounds that hold promise is WR2721, which appears to offer good protection for bone marrow, skin, kidney, gastrointestinal tract, and salivary glands (Mandell and Wharam 1991).

2.2.2.7 Specific radiation fields

Cranial irradiation
Cranial irradiation is commonly used in the treatment of ALL. The goal of this technique is to deliver tumouricidal doses to the entire intracranial subarachnoid space. The target volume includes the extension of subarachnoid space around the optic nerve, in practice incorporating the orbital apex and the posterior-most aspect of the retina. It is also necessary to include the subfrontal region down to the cribiform plate and the temporal fossa (Figure 2-5). Inclusion of the cribiform plate demands precise field alignment to allow appropriate blocking of the anterior eye and lens. The lower margin is established at the second cervical vertebra (Kun and Moulder 1993).

Craniospinal Irradiation
Craniospinal Irradiation is one of the most technically demanding techniques in radiotherapy. The goal is homogeneous irradiation of the subarachnoid space, including the intracranial and spinal meninges. The target volume for the cranium is identical to that discussed for ALL; inclusion of the posterior orbit for primary CNS tumours appears to be unnecessary. Inclusion of the cribiform plate is critical; failure at this site has been documented commonly in medulloblastoma. The target volume for the spine includes the entire length of the subarachnoid space at least to the bottom of the thecal sac at the level of the second sacral vertebra (Kun and Moulder 1993).
Figure 2-5  Cranial irradiation. Clinical illustration of the radiation field (A) and radiographic illustration of the radiation field (B)
Figure 2-6

Common fields of radiation therapy for tumours of head and neck
Solid lines show common field.
Dotted lines indicate fields when increased dosage is used.
F, Field for lymphatics of neck.
(Source: Engelmeier and King 1983)

Head and Neck Irradiation

Radiation therapy for tumours of the head and neck region differs with the tumour site and histology. Careful definition of treatment volume requires CT imaging. For most paediatric applications (e.g., soft tissue sarcomas, nasopharyngeal lymphoepithelioma), tumouricidal doses exceed the normal tolerance of the spinal cord. The target volume often includes tissues adjacent to the orbit(s) or base of the skull. Multiple treatment fields and coordinated use of photons and electrons are necessary to achieve the desired target volume dose while observing normal tissue tolerance (Kun and Moulder 1993). Common fields of head and neck irradiation are presented in Figure 2-6.
Abdominal Irradiation
For cancers requiring whole-abdominal irradiation, such as Wilms' tumour, malignant lymphoma, and ovarian neoplasms, it is important to include the entire peritoneal cavity. The treatment volume extends from above the diaphragm superiorly to the obturator foramen inferiorly. Customised blocks permit shielding toward the cardiac apex and of the acetabulum and femoral heads. Whole abdominal irradiation is limited by the need to block the kidneys (at 1400 to 1800 cGy) and at least a portion of liver (at 1800 to 2400 cGy), (Kun and Moulder 1993).

Extremity Irradiation
Irradiation of extremity lesions is often more difficult than complex field arrangements for the head and neck region. Treatment fields must encompass the tumour region, often involving a considerable length of the extremity. It is critical to exclude a strip of tissue at least 1 to 2 centimetres wide along the entire length of the irradiated extremity to avoid sclerosis of the dermal lymphatics, which may follow irradiation if the entire circumference of the extremity is subtended (Jentzsch et al 1981).

Lung Irradiation
The important factors in the whole-lung irradiation include volume definitions and prior abdominal irradiation. The treatment fields should extend to cover the lung bases inferiorly, usually to the level of the eleventh or twelfth thoracic vertebra. Caution must be exercised in children previously treated to the abdomen, noting the limits of liver and kidney tolerance depending on the previous irradiation volume, the presence of one or both kidneys, and the interval since prior therapy (Kun and Moulder 1993).

Total Body Irradiation (TBI)
TBI can be used for the palliation of children with widespread metastases of malignancies, such as acute leukaemia and neuroblastoma. It is more commonly employed as a part of the preparatory regimen for both malignant and non-malignant diseases when bone marrow transplantation is planned. The treatment fields involve the entire bony skeleton, the marrow cavities, or both (D'Angio 1992b).
2.2.3 Chemotherapy

2.2.3.1 Definition

According to Weiden (1986), chemotherapy refers to the use of any chemical of known composition in the therapy of any illness. The term was originally defined by Paul Erhlich at the beginning of this century in the treatment of parasite and other infectious diseases. In general usage today, however, chemotherapy has come to refer specifically to the treatment of malignant disease with antineoplastic drugs. Some drugs of wide use (for example, hormones) are occasionally included while others, albeit of more restricted use (for example, biologic response modifiers) are generally excluded.

2.2.3.2 Origins

The first anticancer drug introduced into clinical trial was nitrogen mustard (methylbis[chloroethyl]amine hydrochloride). Sulfur mustard was originally synthesised in 1854 and was used in World War I as an offensive weapon when it was found that very low concentrations could effectively incapacitate unprotected combat troops by causing irritation of the respiratory tract and eye. It was soon recognised that sulfur mustard also had effects on the rapidly dividing cells of the gastrointestinal tract and blood forming organs. As early as 1935 Berenblum had recorded that mustard gas could impede the development of chemically induced tumours in animals. However, the question of whether the mustard agents might be used to destroy a tumour before it destroyed the host was first formulated by two young pharmacologists at Yale University, Alfred Gilman and Louis S. Goodman. They conducted animal studies on the toxicity and pharmacokinetics of intravenous (IV) nitrogen mustard and showed that it could produce remission of murine lymphoma. The first clinical trial of nitrogen mustard was conducted by Gustav Lindskog at Yale in 1942 on a patient with rapidly progressive malignant lymphoma who achieved a complete although transient remission. Several clinical trials soon confirmed the effectiveness of nitrogen mustard in the treatment of malignant lymphoma as well as some epithelial tumours and the era of the modern cancer chemotherapy was born (Einhorn 1985).
The use of drugs to treat childhood cancer began about 1947 when Farber and colleagues reported that aminopterin, a folic acid antagonist, produced remission in acute leukaemic children. Since then there has been intensive activity both to discover new drugs and also more effective schedules for using existing drugs. Nevertheless, it is worth noting that many drugs presently used in the treatment of childhood cancer were available 20 years ago. The early use of cytotoxic drugs was as single agent. Nowadays, they are generally used in combination, often in complicated protocols which make use of the understanding of their modes of action and also of cell cycle kinetics (McWhirter and Masel 1987 p 52).

2.2.3.3 Cell cycle kinetics

All cells, both normal and neoplastic, grow and divide through a series of biochemical events known as the cell cycle. It is generally divided into four stages (Figure 2-4). The $G_1$ phase begins as a cell is preparing to proliferate. It is a period of active RNA and protein synthesis, especially of the enzymes necessary for DNA synthesis. During the next, or $S$, phase DNA synthesis takes place, resulting in a doubling of cellular DNA content. There then follows a second gap, or $G_2$ phase. This is a period of RNA and protein synthesis required to construct a mitotic apparatus and begin cell division. Finally the cell enters the mitotic, or $M$ phase which consists of spindle formation, separation of chromosomes, and actual cell division (Weiden, 1986). At this point the cell divides into two daughter cells and faces one of three possible fates (Close and D'Angio 1992):

1. It may embark upon another proliferation cycle by entering $G_1$;
2. It may enter $G_0$ or the resting phase.
3. It may 'leave' the cell proliferation cycle by becoming totally differentiated or by dying.

Normal cell growth is carried out under the control of a set of complex regulation mechanisms that keep cell populations at optimal numbers. Cancer occurs when one or more cells lose one or more of these growth controls and begin to proliferate unchecked (Close and D'Angio 1992).
2.2.3.4 Growth kinetics

Most tissues in human body have a small percentage, or growth fraction, of their cells actively dividing at a given time. Most cells are in the G₀ or resting phase, being called into G₁ for repair of injury or in response to a metabolic demand. Brain, kidney, lung, and liver tissue have the smallest growth fractions, while tissues such as gastrointestinal epithelium and haematopoietic stem cells have relatively more active or larger growth fractions.

Tumours also have some variability in their relative growth fractions; more cells of malignant processes such as leukaemia and lymphoma are dividing than those of most soft tissue or brain tumours. In general, the larger the growth fraction, the more susceptible the neoplastic cells are to chemotherapeutic agents designed to inhibit DNA synthesis or to interfere with progression through other phases of the cell cycle. Tumours that have a large portion of their cells resting in G₀, protected from cell cycle specific agents, are more resistant to chemotherapy. The G₀ cells have unlimited growth potential and can be recruited into G₁ to repopulate the tumour under certain conditions (Close and D'Angio 1992).

2.2.3.5 Classification

According to Weiden (1986), chemotherapeutic agents can be classified, in relation to dependence of their activity on cell cycle and proliferative state, into 3 classes:

Class I Cell-cycle-nonspecific agents

These agents are effective whether cells are resting or in cycle. These include nitrogen mustard and the nitroureas.

Class II Cell-cycle-specific phase-specific agents

These drugs are most active against cells in only one phase of the cell cycle, for example:

- G₁: Enzymes such as asparaginase
- S: Antimetabolites such as methotrexate
- G₂: Some antibiotics such as bleomycin and etoposide
- M: Spindle cell inhibitors such as vinblastine and vincristine.
Class III Cell-cycle-specific phase-nonspecific agents

These agents are effective while cells are in cycle, but are not dependent on their being in a particular phase. These include most of the alkylating agents and antitumour antibiotics.

This classification, although not absolute, helps in the understanding and designing of chemotherapy programs. For example, cell-cycle-specific phase-specific agents would unlikely to be effective against cell populations with a slow turnover or a high percentage of dormant cells. Rather, cell-cycle-nonspecific agents would be preferred for such slow-growing tumours. Moreover, if phase-specific agents were used a higher dose would be less likely to kill more cells (since only those cells in a sensitive phase would be killed) than would prolonged or repeated exposure to the drug (to allow more cells to enter the sensitive phase of the cell cycle) (Weiden 1986).

Chemotherapeutic agents are also frequently divided into four major groups (Weiden 1986, Vietti 1991, Close and D'Angio 1992, Balis et al 1993): alkylating agents; antimetabolites; antitumour antibiotics; and plant alkaloids.

Alkylating agents

The alkylating agents are an important group of anticancer drugs that have a broad range of clinical activity. In general, these drugs are chemically reactive compounds that exert their cytotoxic effect through the covalent bonding of an alkyl group (i.e., alkylation) to important cellular macromolecules, especially DNA. Although a number of nucleophilic molecules and their subunits are alkylated intracellularly, damage to the DNA template and inhibition of DNA synthesis appear to be the major determinants of cytotoxicity (Balis et al 1993).
As a class, because they interact with preformed molecules, the alkylating agents are not phase specific (class III) and some are cell cycle nonspecific (class I) (Weiden 1986). The alkylating agent can also be subdivided into two groups: classic and nonclassic alkylating agents. Classic alkylators include nitrogen mustard, cyclophosphamide, nitrosoureas and their derivatives. Nonclassic alkylating agents include platinum compounds (i.e., cisplatin, carboplatin), dacarbazine (DTIC), and procarbazine (Balis et al 1993).

Antimetabolites

The antimetabolites are close structural analogues of vital intermediates in the biosynthetic pathways of nucleic acids and proteins. By acting as fraudulent substrates for the enzymes in these various pathways, antimetabolites either inhibit synthesis of cellular macromolecules and their building blocks or are incorporated into the macromolecules, resulting in a defective product (Balis et al 1993). There are three ways in which these agents or their biotransformed active products exert their effects (Weiden 1986):

a) by substituting with a normal metabolite when the product containing the substitute molecule is functionally inadequate;
b) by competing with a normal metabolite for the occupation of the catalytic site of a key enzyme; or
c) by competing with a normal metabolite that acts at a noncatalytic site to alert the function of a key enzyme.

Because of the primary effect on DNA synthesis, these agents are largely cell-cycle-specific phase-specific (class II) and their effectiveness is often critically dependent on schedule of administration (Weiden 1986).

Antimetabolites important in the treatment of paediatric cancers include the folate analogue methotrexate, the purine analogues 6-mercaptopurine and 6-thioguanine, and the pyrimidine analogues cytarabine and 5-fluorouracil (Balis et al 1993).
Antitumour antibiotics
Most of the current antitumour antibiotics are naturally occurring substances that were originally isolated from the microbial broth of a variety of species of the group of soil inhabiting micro-organisms known as Streptomyces. The agents from this class of anticancer drugs used in the treatment of childhood cancers include the anthracyclines, dactinomycin, and bleomycin.

All produce their effect by binding to and thereby damaging DNA. Dactinomycin and the anthracyclines (doxorubicin and daunorubicin) intercalate between DNA base pairs and thus inhibit DNA-dependent DNA and RNA synthesis. Bleomycin causes DNA strand scission. In general, the kinetics of their cytotoxic effect is that of cell-cycle-specific phase-nonspecific (class III) agents (Weiden 1986).

Plant alkaloids
Two of the most used chemotherapeutic agents, vincristine and vinblastine, are derived from the periwinkle plant. These vinca alkaloids are stathmokinetic agents. They are inhibitors of microtubular protein formation and thus interfere with the development of the mitotic spindle, resulting in metaphase arrest. Although difficult to classify, both are generally regarded as cell-cycle-specific phase-specific agents (Weiden 1986).

The epipodophyllotoxins are semisynthetic derivatives of podophyllotoxin which was extracted from the roots and rhizomes of the May apple, or mandrake (Balis et al 1993). Etoposide (VP-16), the first active agent in this group, and tenoposide have no effect on microtubules but exert their anticancer effects through inhibition of DNA synthesis and strand breaks (Close and D'Angio 1992).
Other miscellaneous agents which do not fit into the above categories are:

**Corticosteroids**

Although they are not generally thought of as anticancer drugs because of the diversity of their other clinical uses, the corticosteroids (i.e., cortisol, prednisone, prednisolone, dexamethasone) play a significant role in treatment of ALL, lymphoma, and Hodgkin's disease and have been incorporated into treatment regimens for histiocytosis and brain tumours. Corticosteroids do not have only anti-inflammatory effects but also lymphyolytic effects against lymphoid growth. The mechanism of lymphyolytic effect, although not clearly defined, appears to be mediated through glucocorticoid receptors (Balis et al 1993).

**L-Asparaginase**

L-Asparaginase is an enzyme that provides selective nutritional therapy for ALL and the lymphomas. This enzyme catalyses the conversion of the amino acid L-asparagine to aspartic acid and ammonia, rapidly depleting the circulating pool of L-asparagine. In most tissues, this non-essential amino acid can be synthesised from aspartic acid and glutamine by enzyme asparagine synthase. However, sensitive lymphoid malignancies have low levels of this synthetic enzyme and depend on the circulating pool of L-asparagine as a source of this amino acid. Depletion of circulating L-asparagine by L-asparaginase leads to the selective antileukaemic effect of this drug. Depletion of L-asparagine with leukaemic cells results in inhibition of protein synthesis, which accounts for the cytotoxicity of this agent (Balis et al 1993).

**2.2.3.6 Mechanism of action of anticancer agents**

In general, the nucleic acids and cytoplasmic proteins are the targets of antineoplastic agents in complex interactions. These include inactivation of nucleic acids, interference with their biosynthesis, and disruption of vital protein structures associated with cell division. Close and D'Angio (1992) summarised the drug mechanisms of action as shown in Figure 2-7.
2.2.3.7 **Roles of chemotherapy**

From the clinical viewpoint, chemotherapy holds three major roles in cancer treatment: cure, with or without the use of other modalities, palliation, and prevention. The prophylactic use of chemotherapeutic agents to prevent the development of cancer is still largely experimental but not entirely so. One example is sunscreen which is used to shield individuals from solar radiation to prevent the development of skin cancer, especially those with xeroderma pigmentosa (Vietti 1991).

Chemotherapy can be used as palliation where it is clear that the patient cannot be cured by chemotherapy or any other form of treatment. The objectives of using chemotherapy for these cases, e.g., leukaemia after one or more relapses, are to relieve symptoms and produce a useful prolongation of life (McWhirter and Masel 1987 p 55).
For curative purpose, chemotherapy may be used either as the sole method of treatment or as adjunct in multimodal therapy. To accomplish the ultimate goal, achieving long-term survival or cure, several strategies of chemotherapy have been developed.

**Combination chemotherapy**

With the exception of African Burkitt's lymphoma, for which cyclophosphamide alone has been curative, better anticancer effects are usually achieved by using two or more drugs in combination. The importance of administering anticancer drugs in combination was first appreciated in the treatment of acute lymphoblastic leukaemia. Because of marked improvement in survival after combination chemotherapy, several multidrug regimens have currently been designed for a number of childhood cancers, such as LSA₂L₂ regimen for non-Hodgkin's lymphoma, and a seven-drug regimen (the T10 protocol) for osteosarcoma (Close and D'Angio 1992).

The primary rationale for the use of combination chemotherapy is to overcome drug resistance to individual agents. Most of the multiagent regimens employ drugs with different modes of action and toxicities to provide additive or synergistic cytotoxic effects against the tumour cell population while minimising host toxicity (Vietti 1991).

Chemotherapy can be administered by different methods of administration, e.g., per oral, intramuscular, or intravenous injection. This is generally designed by considering the type of therapeutic agents, the accessibility of the tumour cell to the drugs and the consequent host toxicity.

The limited distribution or penetration of the various anticancer drugs into the central nervous system is of particular concern in treatment of childhood cancer because primary and metastatic tumours are common in children and because current treatment regimens are associated with acute and chronic neurotoxicity. Intrathecally injected chemotherapy (e.g., methotrexate, cytarabine) and high-dose systemic therapy are possible approaches to circumvent this problem (Balis et al 1993).
2.2.3.8 Multimodal therapy

Multimodal therapy is concurrent or sequential use of more than one major method of treatment. At present, four forms of treatment are utilised clinically: surgery; radiotherapy; chemotherapy; and, to a very limited extent, immunotherapy. In general, the objectives of any multimodal program are to obtain the maximum therapeutic effect and, at the same time, to avoid serious acute and long-term complications (Vietti 1991).

Chemotherapy plays a role in providing backup if another mode of treatment fails to kill all malignant cells or it will result in unacceptable sequelae. Chemotherapy appears to be most effective when administered in the adjuvant setting, immediately after local therapy with surgery or radiation because it prevents metastatic recurrence by eliminating micrometastatic tumour deposits that may be present in the lungs, bone, bone marrow, lymph nodes, and other sites. This approach may, however, enhance the adverse effects of local therapy to the normal tissue. One strategy to avoid delays caused by potential adverse interactions between chemotherapy and surgery or irradiation is the administration of the drug therapy before definitive local therapy. This approach is called primary or neoadjuvant chemotherapy (Balis et al 1993).

In addition, chemotherapy is commonly a part of the preparatory regimen, in combination with total body irradiation, for the patient who needs to have bone marrow transplantation. In patients with malignancy, the use of chemotherapy therefore aims both to suppress the immune response to prevent rejection of the graft and to totally eradicate the malignant cells (Johnson 1991).
2.2.4 Specific Treatment

In most childhood cancer, all three principle modalities will be employed to form a specific protocol or treatment plan. In general, treatment protocols vary upon the nature of cancer. The treatment plans for a particular type of cancer, although similar in principle, are divergent due to many parameters such as:

- stage of disease at the time of diagnosis,
- protocols, available at the time of diagnosis,
- protocols, practised in a particular specialised centre.

This discussion concentrates on the general concept of management method for common childhood cancer. The details of treatment protocols for common childhood cancers, used at the Royal Alexandra Hospital for Children, are described in the Appendix I.

Acute Leukaemias

The treatment of acute leukaemias varies with the clinical risk features. The basic components of a treatment program include:

- initial induction therapy with combination chemotherapy until the bone marrow no longer shows leukaemic cells;
- prophylactic treatment to the central nervous system, with intrathecal or intravenous chemotherapy and/or cranial irradiation; and
- a continuation of systemic treatment (maintenance) with multiagent chemotherapy for 2-3 years (Behrman 1992).

Hodgkin's disease

Both radiation therapy and chemotherapy are highly effective in the treatment of Hodgkin's disease. The treatment strategy varies upon the staging of the disease. Radiation alone has been used traditionally to cure stage I, II, and III disease. It entails moderately high doses of 3600-4400 cGy. The upper torso is irradiated for supradiaphragmatic Stage I disease using the 'mantle' field, the extended field for stage II (Figure 2-8), and total nodal irradiation for Stage III patients. Total nodal irradiation adds the iliac, inguinal and femoral lymph node chains to the extended field (Behrman 1992, Lange 1992).
Line et al (1979) found that the lateral scattered radiation from mantle field irradiation delivered a dose of approximately 400-1000 cGy to the tooth buds and mandibular growth centres. They concluded that scatter from mantle radiation field is significant to alter or retard development of the teeth and impair mandibular growth centres, even though not directly in the treatment field.
Chemotherapy was reserved for patients with Stage IIIIB or Stage IV disease or for patients who relapsed after radiation therapy. The four-drug regimen, either with MOPP [mechlorethamine (nitrogen mustard), vincristine (Oncovin), prenisolone, and procarbazine] or with ABVD [doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine] can produce long disease-free periods for patients with advanced Hodgkin's disease. These regimens have been used either alone or combined by alternating six courses of MOPP with six of ABVD. The combination of each regimen with irradiation to involved areas has also been indicated (Behrman 1992, Lange 1992).

Non-Hodgkin's lymphoma

Surgery may play an important role in removing bulk disease in primary intestinal tumours. It is also needed when acute intussusception is present; otherwise operations are not warranted because the results of chemotherapy are excellent. For localised lymphoma, treatment is similar to that of ALL, but lasting only 6 months and with no irradiation. In general, the treatment of non-Hodgkin's lymphoma comprises of three components like that of ALL, but with shorter duration of maintenance. Several regimens have proved to be effective in achieving remission. The ten-drug regimen (LSA₂L₂) is one of many effective regimens for lymphoblastic lymphoma while the COMP (cyclophosphamide, oncovin, methotrexate, and prednisolone) is more effective in nonlymphoblastic lymphoma (Behrman 1992, Lange 1992).

Central nervous system tumours

The management of the central nervous system tumours varies with the histopathologic classification of tumours. Surgical excision is usually conducted wherever possible. Radiotherapy is generally used postoperatively in the cases where complete excision is impossible. Irradiation to the entire neuraxis, from the cerebral hemispheres to the cauda equina, is commonly necessary in treatment of medulloblastomas because of their propensity to metastasize within the central nervous system. Several chemotherapeutic regimens have also been used as part of treatment in most cases due to the difficulties of determining the correct radiation field and dose together with the poor results of radiotherapy, with or without surgery (McWhirter and Masel 1987 p 168).
Neuroblastoma
Different treatments are needed for different clinical stages of disease. In Stages I and II, a complete excision without radio- or chemotherapy may be possible. For other Stages, schedules may include preoperative treatment with chemotherapy and/or radiotherapy, followed by excision of the primary tumour. High-dose chemotherapy and bone marrow transplantation may also be employed (Voûte et al 1992).

Wilms' tumour
Total nephrectomy is the key step in treatment of Wilms' tumour. There are two different approaches to management of children with Wilms' tumour; pre- versus postoperative therapy. Preoperative radiotherapy or multiagent chemotherapy is given to shrink the tumour and make operative removal easier. The other approach employs early surgery and all treatments are given postoperatively (D'angio 1992a).

Rhabdomyosarcoma
Rhabdomyosarcoma is rarely completely resectable. The treatment program for each patient is usually designed according to the location and stage of the disease. Chemotherapy may be used prior to surgery to reduce the amount of surgery required. A regimen involving local irradiation and systemic chemotherapy, following the complete local excision, may be needed to destroy subsequent metastatic disease. Intrathecal therapy is generally given to patient with primary disease in parameningeal sites (nasopharynx, nasal cavity, paranasal sinuses, middle ear, mastoid, or pterygopalatine or infratemporal fossae) (Behrman 1992).

Osteosarcoma
For the patient with no evident metastatic disease, the recommended treatment is radical surgery. Osteosarcoma is not radiosensitive therefore chemotherapy is the only useful means to improve survival (Behrman 1992).

Ewing sarcoma
In general, amputation is not recommended in patients with Ewing sarcoma because the tumour is sensitive both to radiation and chemotherapy. High-dose irradiation and combination chemotherapy is recommended. Active agents are dactinomycin, doxorubicin, cyclophosphamide, and vincristine (Behrman 1992).
Retinoblastoma

Treatment of retinoblastoma is very specialised and cases should be referred to an appropriate centre. Older children with non-familial, sharply circumscribed, localised lesions can be managed by cryosurgery, photocoagulation, or radioactive plaques. The tumours are highly radiosensitive and can be activated by doses of 4000-4500 cGy. Radiation therapy is therefore the treatment of choice for many patients with familial but localised intraocular tumours with normal intraocular pressures. Patients with extensive tumours where useful vision cannot be preserved, or with localised but non-radioreponsive tumours, will require enucleation of the affected eye. No further treatment is indicated for those whose the tumour is confined to the retina. For more extensive tumours, adjuvant combination chemotherapy and orbital radiotherapy will be given (Sinniah and Meadows 1992).

2.2.5 Late Effects of Childhood Cancer Therapy

Significant advances in childhood cancer have led to dramatic improvement in survival. Antineoplastic therapy is not specific for tumour cell but affects normal cells as well; therefore, all cancer treatment modalities are associated with toxicities. Some of these toxicities occur early while others present months to years later. As children with cancer are surviving longer, the incidence of long-term sequelae of cancer therapy has increased.

Late effects in survivors of childhood cancer may be the result of genetic abnormalities which predisposed towards the cancer, of the cancer itself, or of its treatment. In some cases these effects may be combined. It may, therefore, be impossible to define with certainty the cause of the late effects (McWhirter and Masel 1987 p 291). The follow-up of long-term consequences of cancer treatment in children is increasingly a point of interest in many institutions. It is frequently studied by organ system and in relationship to oncogenesis. The following discussion will summarise the common late effects of treatment of cancer in children.
2.2.5.1 Cardiovascular system
Late effects on the cardiovascular system are the most serious complications of cancer treatment. In children, cardiomyopathy, congestive heart failure, and pericarditis are the most frequently observed cardiovascular dysfunctions. These complications occur commonly following chemotherapy with the anthracycline drugs and radiation therapy to the mediastinum (Byrd 1985).

2.2.5.2 Endocrine system
Late abnormalities in the endocrine system secondary to antineoplastic therapy are manifested in three areas: hypothalamic-pituitary axis; thyroid gland; and gonads.

Most complications associated with the hypothalamic-pituitary axis are secondary to radiation therapy for brain tumours, head and neck tumours, and central nervous system prophylaxis in children with acute leukaemia. Endocrine abnormalities range from isolated growth hormone deficiency to panhypopituitarism, with growth hormone deficiency being the most common abnormality (Byrd 1985, Herber et al 1985).

Incidence of neuroendocrine dysfunction depends on the age of the child, dose of radiation given and techniques used. Younger children who receive radiation doses of more than 3000 rads are at greatest risk (Byrd 1985). Chemotherapeutic protocol is also noted to contribute to growth retardation in ALL (Clayton et al 1988).

Hypothyroidism, nodular abnormalities, and carcinoma are the most common complications in long-term survivors of childhood cancer who receive radiation to the thyroid gland (Byrd 1985, McWhirter and Masel 1987 p 294).

Both the ovaries and the testis are at risk for long-term damage from cancer therapy. Gonadal damage may be manifested as infertility or by hormonal dysfunction. Cancer treatment may result in an absence of secondary sexual development and elevated serum gonadotropins with low serum estradiol concentrations in the prepubertal female. In the
postpubertal female, treatment may cause amenorrhea, oligomenorrhea, and menopausal symptoms. In the postpubertal male, there are often no signs and symptoms. Gonadal damage may result from tumouricidal doses of radiation to gonads and some chemotherapeutic agents, particularly alkylating agents (Byrd 1985).

2.2.5.3 Gastrointestinal system
Both chemotherapy and radiation therapy may affect the gastrointestinal system. The major late sequelae of cancer therapy are hepatic injury following chemotherapy or radiation therapy.

The hepatic injury may be hepatic dysfunction, fibrosis, and/or cirrhosis. Several chemotherapeutic agents are known to produce signs of transient hepatotoxicity, but long-term liver damage is most commonly associated with methotrexate and 6-mercaptopurine therapy (Nesbit et al 1976).

2.2.5.4 Musculoskeletal system
Musculoskeletal abnormalities are the most common among the late sequelae of cancer therapy (Meadows et al 1992). They may result from either radiation therapy or chemotherapy, or the combination of these. The effects observed are related to the age of the patient at the time of treatment, the site treated, and the dose, schedules, and source used. These complications include some degree of bone, muscle, and soft tissue deformities, scoliosis, kyphosis and osteoporosis (Byrd 1985).

2.2.5.5 Nervous system
Long-term neurotoxicity may occur after cancer treatment. This toxicity may be manifested as an encephalopathy, peripheral neuropathy, or neuropsychological and intellectual dysfunction (Byrd 1985). It was reported that children with leukaemia, receiving 2400-cGy cranial irradiation can develop declines in IQ of approximately 20 points and are delayed in scholastic achievement by approximately 2 years (Meadows et al 1981, Peckham et al 1988). Recently, Meadows et al (1992) also noted more severe
cognitive deficits among patients cranially irradiated for leukaemia prophylaxis with 2400 cGy compared to 1800 cGy.

Brouwers et al (1985) reported brain abnormalities, including cortical atrophy and intracerebral calcification, in 13 of 23 long-term survivors of childhood ALL. The patients with brain abnormalities had greater neuropsychologic deficits, such as memory loss and increased distractibility, than those without abnormalities.

2.2.5.6 Pulmonary system

The major late effects of cancer therapy on the lungs are interstitial pneumonitis and pulmonary fibrosis. Both chemotherapy and radiation therapy have been associated with pulmonary toxicity. The most important predisposing factors to the development of these complications are radiation dose and the volume of lung irradiated. The major drugs reported to be associated with pneumonitis are the nitrosoureas, bleomycin, busulfan, cyclophosphamide, and methotrexate. Dactinomycin or anthracyclines may also enhance pulmonary toxicity (Byrd 1985).

2.2.5.7 Secondary malignancies

The risk of developing second malignant neoplasm is clearly increasing in children surviving cancer. The factors that predispose to this serious complication include genetic predisposition and therapy, and among the therapeutic agents, radiation, alkylating agents and anthracyclines are implicated (Meadows et al 1992).
2.3 DENTAL DEVELOPMENT

Numerous publications have described the formation of dental tissues with a myriad of
detail at both gross and molecular levels. This discussion provides a brief summary of the
most recent and relevant material on the development of human teeth and associated
abnormalities.

Human beings develop two different dentitions, namely, the deciduous (primary) and the
permanent (secondary) dentition. Both are derived from ectoderm and mesoderm and
pass through the same process of tooth formation, although at different times. The
formation of the dentition is a continuous process, however, it is divided into several
stages for ease of description. These stages are:

- initiation or bud stage,
- histodifferentiation or bell stage,
- morphodifferentiation,
- apposition,
- calcification, and
- eruption.

The initiation stage is the stage at which the dental lamina can be identified separately
from the oral ectoderm. The dental lamina proliferates to form a series of epithelial
ingrowths (tooth buds) into the ectomesenchyme. The dental lamina provides tooth
germs not only for the twenty primary teeth but also for the thirty-two permanent teeth.
The tooth germs for the successional permanent teeth (incisors, canines and premolars)
form as a result of further proliferative activity within the dental lamina on the lingual
aspect of the deciduous tooth germs, during the bell stage. The tooth germs for the non
successional permanent teeth (molars) originate from the dental lamina which grows
distally in the dental arch after finishing the formation of the primary tooth germs
The entire primary dentition is initiated between the sixth and eighth week of embryonic development, the successional permanent teeth between the twentieth week in utero and the tenth month after birth, and the non-successional permanent teeth between the twentieth week in utero for the first molar and the fifth year of life for the third molar (Ten Cate 1989). The dental lamina, therefore, is active over a period of approximately 5 years after birth.

In the proliferation or cap stage, the epithelial ingrowth continues to proliferate and changes morphologically from the bud stage into the cap stage. It is now called the enamel organ. The ectomesenchyme adjacent to the epithelial ingrowth, immediately increases cellular density to form the dental papilla. The condensed ectomesenchyme which bounds the dental papilla and encapsulates the enamel organ is called the dental follicle.

In the bell stage, the enamel organ has multiplication, growth, differentiation, and rearrangement until it has four definite layers, including the outer enamel epithelium, the stratum intermedium, the stellate reticulum and the inner enamel epithelium. The dental lamina in this stage is separated from the enamel organ by a cell-free zone. Another important event is that the developing tooth germ is disconnected from the oral epithelium with the breaking up of the dental lamina joining the tooth germ to the oral epithelium.

During the advanced bell stage, the morphologic pattern or basic form and relative size of the future tooth is established by morphodifferentiation. The dentinoenamel and dentinocemental junctions, which are different and characteristic for each type of tooth, act as a blueprint for the deposition of the matrix of the hard dental structures (Bhaskar 1986).
The *oppositional stage* is characterised by the deposition of the matrix of the dental hard tissues: dentine, enamel, and cementum. The formation of enamel and dentine are interdependent processes. The morphologic change of the cells of the inner enamel epithelium induce the adjacent undifferentiated ectomesenchymal cells in the dental papilla to differentiate into odontoblasts, the dentine-forming cells. Immediately after the formation of the first dentine, the cells of the inner enamel epithelium differentiate into ameloblasts and begin producing enamel matrix. This is known as reciprocal induction. These cell differentiations start from the cuspal tip and proceed in a cervical direction.

After enamel and dentine formation has reached the future cementoenamel junction, the development of the root(s) begins. The enamel organ plays an important role in root development by forming Hertwig's epithelial root sheath, which molds the shape of the roots and initiates dentine formation. Once the first layer of dentine has been laid down, the epithelial root sheath loses its continuity. This allows the connective tissue of the dental follicle, surrounding the sheath, to contact with the outer surface of the dentine and to differentiate into cementoblasts which deposit a layer of cementum onto the surface of the dentine (Bhaskar 1986).

The calcification or mineralisation of enamel and dentine commences promptly after matrix formation or concomitantly with matrix secretion. It starts firstly with the incisors at about the fourth month in utero and progressively involves the primary canine and molars. All of the primary teeth, therefore, have begun to mineralise by the twenty-eighth week in utero. At birth, the majority of the primary incisors, one third of the crown of primary canines and the cusps of the primary molars have been completed (Massler et al 1941). In the permanent dentition, only the first permanent molars begin mineralisation at birth. The mineralisation of permanent teeth progresses sequentially until completion at about 20 years of life (Table 2-6).
The process of maturation generally describes the final phase of enamel mineralisation which is a slow process of degradation of organic matrix and deposition of mineral content. It regularly occurs during the stage of enamel formation and persists through the time of tooth eruption until the enamel reaches it final high level of mineral content (Stewart et al 1982).

The eruption time of primary teeth is not associated with sex or race. There is no difference between left and right sides, but the mandibular central incisors tend to appear before the maxillary ones. On the other hand, both sex and race variations in eruption time of permanent teeth are reported. Females tend to erupt permanent teeth earlier than males. The differences range from 2 months for the first molar to 10 months for the maxillary canines. North American Caucasians erupt teeth at a slightly later age than do Lithuanians, Puerto Ricans, Negroes and Navahoes. Central American Indians erupt incisors slightly later age than North American Caucasians but posterior teeth slightly earlier. However, racial differences in eruption seldom exceed 6 months (Stewart et al 1982).

2.3.1 Developmental Abnormalities of Teeth

The human dentition has the most prolonged period of development, from the twenty-eighth day of gestation to about the twenty-fifth year of age. Therefore it is not surprising that a variety of developmental abnormalities of teeth frequently appear in children and adolescents. Developmental aberrations may affect the number, shape, structure, and eruption of the teeth and their effect depends upon the stage of development of the dentition. The following discussion will introduce examples of various types of developmental defects in permanent teeth which have been reported as being associated with the treatment of childhood cancer.
<table>
<thead>
<tr>
<th>Tooth</th>
<th>Initiation, month</th>
<th>Calcification begins</th>
<th>Crown completed, year</th>
<th>Eruption, year</th>
<th>Root completed, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxilla</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Central incisor</td>
<td>5–5⅓ in utero</td>
<td>3–4 months</td>
<td>4–5</td>
<td>7–8</td>
<td>10</td>
</tr>
<tr>
<td>Lateral incisor</td>
<td>5–5⅓ in utero</td>
<td>1 year</td>
<td>4–5</td>
<td>8–9</td>
<td>11</td>
</tr>
<tr>
<td>Canine</td>
<td>5½–6 in utero</td>
<td>4–5 months</td>
<td>6–7</td>
<td>11–12</td>
<td>13–15</td>
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<tr>
<td>First premolar</td>
<td>Birth</td>
<td>1½–1⅔ years</td>
<td>5–6</td>
<td>10–11</td>
<td>12–13</td>
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<tr>
<td>Second premolar</td>
<td>7½–8</td>
<td>2–2½ years</td>
<td>6–7</td>
<td>10–12</td>
<td>12–14</td>
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<tr>
<td>First molar</td>
<td>3½–4 in utero</td>
<td>Birth</td>
<td>2½–3</td>
<td>6–7</td>
<td>9–10</td>
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<tr>
<td>Second molar</td>
<td>8½–9</td>
<td>2½–3 years</td>
<td>7–8</td>
<td>12–13</td>
<td>14–16</td>
</tr>
<tr>
<td>Third molar</td>
<td>3½–4 (yr)</td>
<td>7–9 years</td>
<td>12–16</td>
<td>17–25</td>
<td>18–25</td>
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<tr>
<td>Mandible</td>
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<tr>
<td>Central incisor</td>
<td>5–5⅓ in utero</td>
<td>3–4 months</td>
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<td>Lateral incisor</td>
<td>5–5⅓ in utero</td>
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<td>17–25</td>
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</table>
2.3.1.1 Hypodontia (oligodontia)

Hypodontia happens following a disturbance of the initiation and/or proliferation stages. It usually describes the agenesis of one or several teeth (Stewart et al 1982). Hypodontia in the primary dentition is less common than that in the permanent dentition (Stewart et al 1982, Shafer et al 1983). In the permanent dentition, hypodontia is most commonly seen in the third molars. The prevalence of missing one or more third molars varies among different races from 1% in some African Negroes and Australian aborigines, 10-25% in Caucasians, to approximately 30% in Japanese (Stewart et al 1982). The second and third most commonly missing teeth after the third molars are the second premolar (1-2.5%) and the maxillary lateral incisor (1-2%), respectively (Lai and Seow 1989, Gorlin et al 1990).

Interestingly, many studies have found that hypodontia is associated with several other developmental anomalies of the tooth, such as ankylosis or submergence of primary teeth, taurodontia and peg-shaped incisor (Brook,1984, Lai and Seow 1989, der Weide et al 1992).

Aetiology

The cause of congenital absence of teeth is still unclear, although several hypotheses on the basis of genetic and/or environmental influences have been reported.

Genetic factors

-Evolutionary trend

Some investigators believe that the frequency of congenital missing teeth is an intermediate stage of dentitional evolution. They proposed that a dental formula in the future will comprise one incisor, one canine, one premolar and two molars per quadrant (Stewart et al 1982, Shafer et al 1983).

-Monogenic hypothesis

Some investigators have concluded that an autosomal dominant gene is responsible for congenital missing teeth. However, the evidence from several studies in twins and families disagrees with this theory (Boruchov and Green 1971, Gravely and Johnson 1971).
- Component of numerous syndromes

Hypodontia is also frequently found in several syndromes such as ectodermal dysplasia, orofaciiodigital syndrome, Ellis van Creveld syndrome, and cleft lip and cleft palate (Jorgenson 1980).

- Polygenic Model

At present, many findings have shown that this defect is caused by the interaction of many genes with environmental influences (Suarez and Spence 1974, Brook 1984, der Weide et al 1992).

Environmental factors

- Physical disruption of the dental lamina

In the orofaciiodigital syndrome, thick bands of hyperplastic connective tissue attach to developing alveolar area and may cause congenital missing teeth (Stewart et al 1982).

- Space limitation

A spatially constricted area can cause tooth germ regression or agenesis, especially for the third molars (Stewart et al 1982).

- Irradiation

Burke and Frame (1979) mentioned that X-ray irradiation at an early age may destroy the tooth germ, with failure of the tooth to develop.

- Premature birth

Boruchov and Green (1971) showed that premature children (≤ 5 pounds 8 ounces) have a greater incidence of hypodontia.

2.3.1.2 Microdontia

Microdontia results from disturbances during the morphodifferentiation stage. This term describes the tooth that is smaller than normal i.e. outside the usual limits of variation. According to Shafer et al (1983), microdontias are classified into three types:

True generalised microdontia

In this anomaly, all the teeth are well formed but smaller than normal. Apart from its occurrence in some cases of pituitary dwarfism, this condition is exceedingly rare.
Relative generalised microdontia

All teeth in this condition are normal or slightly smaller than normal but they are in jaws that are larger than normal. So there is an illusion of true microdontia. A role for hereditary factors in causing such a condition is suspected.

Microdontia involving a single tooth

This anomaly is more common and affects most often the maxillary incisors and the third molars. The common form of localised microdontia, affecting the maxillary lateral incisor is called "peg lateral". It has a peg-shaped or cone-shaped crown and its root is shorter than usual.

According to Brook (1984), the prevalence of microdontia ranged from 1.9 to 3.1% with a higher proportion of females than males. The study also showed a highly significant association between hypodontia and microdontia. It appeared that the more severe the hypodontia the greater the possibility of clinically apparent microdontia in the same subject.

2.3.1.3 Taurodontism

Taurodontism is an aberration in root structure which is characterised by an apical-occlusal enlargement of the pulp chamber accompanied by a crown of normal configuration. Taurodontism may affect either the primary or permanent dentition. The permanent dentition is more commonly involved. The teeth involved are almost inevitably molars, sometimes only a single tooth, at other times several molars in the same quadrant. The defect may be unilateral or bilateral or may occur in any combination of quadrant involvement. It was found in association with amelogenesis imperfecta. The degree of severity may be related to the number of X chromosomes present (Stewart et al 1982).
Aetiology
This condition appears to be genetically controlled and familial in nature. According to Mangion (1962), several possible causes of taurodontism have been proposed as follows:

1. a specialised or retrograde character
2. a primitive pattern
3. a mendelian recessive trait
4. an anatomistic feature
5. a mutation resulting from odontogenic deficiency during dentinogenesis of the roots.

2.3.1.4 Anomalous root morphology
The aberration in number and/or form of root structures is not uncommon and may affect any tooth, in both primary and permanent dentition. Mongoloid roots are more simple in form than are Caucasian or Negroid roots. Generally, extra canals are recognised in both maxillary and mandibular molars. However published reports also include canines and premolars (Stewart et al 1982, Loh 1990, Christie et al 1991, Hayutin and Ralstorm 1992). As well, Holan and Chosack (1991) reported cases of single rooted molars in the primary and permanent dentition. Double rooted mandibular premolars occur with increased frequency in Turners (XO) syndrome. The most racially distinct trait observed is in mandibular molar roots. It involves an extra distolinguinal root which is frequently seen in Mongoloid groups (Stewart et al 1982).

A common clinical problem posed by the tooth with a supernumerary root is the possible fracture of the extra root. In addition, these anomalous roots may cause other difficulties with endodontic and orthodontic procedures. The stunted growth of the root, premature closure of apices and tapering roots with apical constriction may exist in the patient, exposed to the irradiation at an early stage of development (Burke and Frame 1979, Rosenberg 1990). Brin et al (1991) reported the possible effect of premature extraction of primary molars on the size and length of their permanent successors.
2.4 DENTAL LATE EFFECTS

Thirty years ago, few children in Australia survived cancer and there were very few in whom the long-term effects could be studied. Nowadays with overall survival rates from childhood cancer in the order of 60%, there are increasing numbers of people growing up to be adults who have at some time during childhood suffered cancer.

It is estimated that by the year 2000, one in every 1000 young adults in the third decade of life would be a survivor of childhood cancer. This presumes that 60% of the children with cancer under the age of 15 years can be cured. As approximately one in 600 children will be diagnosed with cancer during childhood, and the cure rate predicted has been borne out in those diagnosed during the 1970s, the following equation can be applied to 20 - 30 year olds:

\[ \frac{1}{600} \times 0.60 = \frac{1}{1000} \] (Meadows et al 1992).

Delayed effects attributable to surgery, irradiation and chemotherapy are being reported with increasing frequency in long-term survivors of childhood cancer. Surgery usually involves ablation of an affected organ, in which circumstance the effect is frequently apparent immediately but also may appear many years later. Chemotherapy induces effects on structures and organs unrelated to the primary tumour because of its systemic distribution. These effects usually appear many years later and include damage to the gonadal, pulmonary, cardiac and nervous systems (Byrd 1985). Similar factors pertain to radiotherapy, however, in contrast to chemotherapy, the effects are usually localised and confined to the radiation field.

Investigation of chronic or delayed dental and maxillofacial complications is a developing aspect in the dental literature. A large mass of relevant information is being generated from animal experiments, reported cases and late effects studies of survivors of childhood cancer. In general, the focus has been on two major aspects: oral health, and dental and maxillofacial abnormalities.
2.4.1 Oral Health

Concern regarding the oral complications induced by cancer chemotherapy and radiotherapy has led to an interest in studying the oral health of patients surviving childhood cancer. The question of whether these children would be more susceptible to dental disease than healthy children has also been raised.

2.4.1.1 Dental caries

Dental caries is a multifactorial disease. It requires a susceptible host, a cariogenic microflora and a suitable substrate which must remain for a sufficient time. Carious lesions develop over a period of months or years. The average time for clinical caries to emerge is $18 \pm 6$ months (Parfitt 1956), although microscopic observations in vivo suggested that greyish-white spots appeared on the enamel within three weeks (Fehr et al 1970).

A program of caries prevention through meticulous brushing and flossing, and follow up dental visits for fluoride prophylaxis, additional cleaning and supplemental fluoride all contribute to a lower caries rate (Rakocz et al 1982).

Radiation dental caries have been well described by del Regato since 1939. It is well documented that caries incidence is high in patients who have received tumourcidal irradiation to the jaws and/or salivary glands (Brown et al 1975, Dreizan et al 1977, Nakamato 1979).

The reasons for the higher incidence of caries in children receiving antineoplastic therapy may lie in the disease itself and/or the therapy and, especially, in the side-effects of the drugs used. Radiation may induce the environmental changes such as xerostomia, lower pH of the saliva, and alteration of the oral flora (Carl et al 1973, Beumer et al 1979).

Some anti-cancer drugs cause transient xerostomia (Ostchega 1980). Cortisone is also cariogenic (Liu and Lin 1968). Pajari (1989), however, reported that some antineoplastic agents such as doxorubicin and methotrexate have produced significantly reduced caries.
prevalence in the rat molars. Some cancer drugs cause vomiting and thus reduce the oral pH and promote dental erosion (Lavelle et al 1984).

The effects of sugar-based medicines on the dental health of sick children have been previously outlined (Hobson 1984). Previous studies have shown that children who take sweetened medicines on a long-term basis have a significantly higher caries experience than control groups (Roberts & Roberts 1979, Feigal et al 1984). Thus, the long-term use of the sugar-based paediatric medicines in cancer patients may increase their caries experience.

Dietary factors are also important. Because of stomatitis, bad taste and painful lesions in the mouth, sweet and cariogenic food may be preferred.

The DMF and dmf indices have been frequently employed in assessing dental caries experience. Several authors have reported that there is no difference in caries rate in the survivors of childhood malignancy, compared with either the general population (Welbury et al 1984, Fleming and Kiniron 1986, Nunn et al 1991) or with controls (Maguire et al 1987, Näsman et al 1994).

Fromm et al (1986) also found that radiation caries was not universal in eight patients with nonsecreting parotids after high dose irradiation.

In contrast, Bertolone and co-workers (1981) reported a slightly higher caries than the national average in a group of American children in remission from ALL. Purdell-Lewis et al (1987) in the Netherlands also found more filled and diseased permanent teeth in the 45 children treated with chemotherapy only. In Finland, Pajari et al (1988a) reported a higher caries prevalence and incidence in children with cancer than in their age and sex-matched controls.
These inconsistent results from the studies of caries incidence in survivors of childhood cancer probably arise from the nature of dental caries which is caused by numerous factors. The quality of tooth structure, oral environment (saliva, fluoride and flora), diet and caries prevention programs may all modify the caries rate.

In children lower dose levels are frequently used and the xerostomia is usually only temporary. Also the salivary gland tissues in children may have more of a regenerative capacity (Gorlin and Meskin 1963, Blozis and Robinson 1968).

2.4.1.2 Periodontal diseases

The adverse effect of radiation on periodontal membrane in kittens, irradiated with 2000 R, has been reported by Donohue and Perreault in 1964. There was a decrease in the width of the periodontal ligament in some areas with the fibres running parallel to the root surface rather than at an acute angle as in the controls. Ankylosis of some teeth was found in 42% of the irradiated animals. Both permanent and primary dentitions showed varying degrees of ankylosis of some teeth in animals that had survived eight months or more. No evidence of ankylosis was found in any of the control animals.

Histologic review of jaw bone specimens from patients who have had resection after canceridal dosages of radiation show findings similar to those reported in animal studies. The periodontal ligament shows a marked acellularity with thickening and disorientation of the protein fibres. The cementum also appears completely acellular, and there are irregularly positioned areas of dentine erosion. Because periodontal structures exposed to canceridal radiation are morphologically and histologically altered, meticulous oral and periodontal hygiene is essential to avoid or minimise periodontal and bone infection (Silverman and Chierici 1965).

The immediate effects of cancer therapy on soft tissue have been well documented (Sonis and Sonis 1979, Childers et al 1993). A 2½ year prospective follow-up study on the incidence of oral complications (including mucositis, ulceration, oral infection, gingival
inflammation and oral bleeding) in 214 paediatric patients with cancer showed that gingivitis is the second most common oral complication. In addition, the rate of gingivitis among patients with leukaemia was five times higher than in patients with sarcoma (Childers et al 1993).

There have been, however, few studies assessing periodontal problems in long-term survivors of childhood cancer. Using the gingival indices of Loe (1967), Welbury and others (1984) found no abnormalities in the soft tissue of 64 survivors of childhood malignancy when compared with the general population.

Fleming and Kinirons (1986) also found that the gingival condition of children in remission from ALL was similar to that found generally in children in Northern Ireland, but that there were increased levels of gingivitis in children receiving chemotherapy compared to those who had completed such therapy. This was similar to the result from the study in 1987 by Maguire and others who reported no difference, in gingivitis and oral hygiene status, between siblings and patients surviving cancer.

### 2.4.2 Craniofacial Growth

It is well documented that radiation disrupts normal development of human skeletal tissue (Donohue et al 1965, Nwoku and Kock 1975). Chemotherapy alone has not been reported as producing aberration in skeletal development in humans. However, the effect on human skeletal development of a combination of radiation and chemotherapeutic agents cannot be excluded. Cancer treatment can disrupt the craniofacial growth both directly and indirectly. Undoubtedly, radiation can cause alteration or death of proliferating cells within or nearby the radiation field. An indirect effect, following radiation and probably chemotherapy, may be an altered hypothalamic-pituitary function resulting in diminished growth hormone production (Blatt et al 1984). This in turn may adversely affect odontogenesis and craniofacial development.
Radiation effect on facial bones results from osteocyte death, microvascular injury, periosteal damage and fibrous replacement of marrow spaces. These changes lead to altered bone growth and development (Nwoku and Kock 1975).

In children, the sensitivity of normal tissue has been estimated to be 25 to 30 percent greater than in adults. This greater sensitivity is related to metabolic activity and corresponds to the periods of most intensive growth, viz., infancy, childhood and puberty (Nwoku and Kock 1975).

In the growing child, the effect of radiation damage is perhaps more conspicuous and more disturbing in the facial skeleton than in the soft tissue. The effects are usually more severe in the mandible than in the maxilla. In most cases, the irradiation of one side leads to damage of the growth centres of that side only, resulting in a unilateral hypoplasia. Damage to both condylar heads will result in a symmetrical micrognathism (Nwoku and Kock, 1975).

The pattern of maxillary deformity is less distinct than in the mandible because it lacks endochondral osteogenesis. Radiation damage may lead to hypoplasia of the maxilla and zygoma, reduction in height, or complete loss of the alveolar ridge and loss of density of the cortical bone (Nwoku and Kock 1975).


Retarded growth of irradiated soft tissue contributes to facial deformity (Donohue 1965). In a review of 41 patients receiving irradiation to the head and face during the growth period, Guyuron et al (1983) found that not only is the growth of soft tissue and bone of the irradiated area noticeably affected, but other parts of the face can also be involved, especially if the dose is to the upper face and the cranial base. They also concluded that
a harmful dose for growing facial bones was 3000 rads. The growing soft tissues may be more sensitive to radiation than bone. Development may be disrupted after as little as 400 rads. In their study, the patients were examined by a plastic surgeon and an orthodontist experienced in facial evaluation. Assessment materials also included colour slides, panoramic and cephalometric radiographs.

Dury et al (1984) reported a case with bimaxillary micrognathia and marked loss of vertical dimension. The mandible was thin and hypoplastic with a small knife-edge alveolar ridge after receiving 4050 rads of irradiation to the right middle ear when the patient was 2 years of age.

In 1984, Jaffe et al described maxillofacial abnormalities exhibiting in 45 long-term survivors of childhood cancer cured with chemotherapy and radiation to the head and neck. No facial deformities were noted in patients with Hodgkin's disease and leukaemia. Patients with other cancer diseases, including sarcoma, brain tumours, retinoblastoma, lymphoepithelioma and histiocytosis, frequently exhibited both facial deformities, for example midface hypoplasia, and abnormal occlusal relationship. No assessment criteria had been clearly defined.

In a study of late effects after combined modality therapy of 20 children with soft tissue sarcomas of the head and neck, Fromm et al. (1986) found some degree of bony or soft tissue deformity in all 16 patients who were younger than, or, 9 years of age at diagnosis. The severe deformity also, notably, developed in those patients who received a tumour dose of ≥ 5000-cGy. The remaining four patients, being 11 years of age or older at diagnosis, had no deformity. Cosmetic evaluation in this study was made subjectively ranking from patients' examinations and their photographic reviews.

Analysing cephalometric radiographs of 17 children undergoing BMT, Dahllöf et al (1989b) reported reduced growth in the craniofacial skeleton in all children conditioned with total body irradiation (TBI) in comparison to the healthy controls. The linear
measurements indicated that high doses of radiation given to growing individuals severely affect the dimensional development of the craniofacial complex. The most pronounced effects were seen in the youngest patients. However, no major effects of TBI were found in craniofacial morphology, nor could any increased tendency for the development of malocclusion be elicited. Children who were not conditioned with TBI exhibited no significant differences when compared to healthy controls in respect of the variables studied.

In a comparative study of identical twins, Berkowitz et al (1989) demonstrated that the affected twin treated with combination chemotherapy and high irradiation dosage had a generalised craniofacial skeletal hypoplasia in the anteroposterior, vertical and transverse planes relative to the normal twin. The observed growth deficits were more severe on the tumour side and the mandible was affected more than the nasomaxillary complex.

Cranial radiotherapy may cause growth hormone deficiency due to disruption of the hypothalamic-pituitary axis (Shalet et al 1976). Many authors have reported abnormal growth hormone secretion in patients who have received central nervous system prophylactic therapy including cranial irradiation (Shalet et al 1976, Danoff et al 1982, Blatt et al 1984, Kirk et al 1987). This may contribute to the abnormalities in growth seen in these patients. The growth of the viscerocranium approximately parallels the general growth curve (Dahllöf et al 1989b). The craniofacial growth disturbances, therefore, may be also indirectly affected by cranial irradiation.

Sonis et al (1990) evaluated 97 children diagnosed with ALL before the age of 10 years and treated with chemotherapy alone, chemotherapy plus 1800-cGy cranial irradiation, or chemotherapy plus 2400-cGy irradiation. Eighteen of 20 (90%) of those patients who received chemotherapy plus 2400-cGy cranial radiation before 5 years of age exhibited a significant deficient mandibular development from the norm. Their study did not mention whether, or how, this deficiency affected the facial appearance of the patient with respect to aesthetic value.
2.4.3 Trismus

The word 'trismus' is derived from the Greek 'trismos', meaning gnashing. It describes a prolonged, tetanic spasm of the jaw muscles by which normal mouth opening is restricted (Tveteras and Kristenson 1986).

Numerous aetiological causes of trismus have been summarised by Luyk and Steinburg (1990) and radiation therapy is one of them.

Post-radiation fibrosis of the muscles of mastication, leading to trismus, is well recognised in adult patients who receive head and neck irradiation involving those muscles of the temporomandibular joint (Montgomery 1977, Engelmier and King 1983, Rothwell 1987). This complication is not immediately apparent following radiation treatment but occurs progressively as mucositis subsides: It may become evident during radiotherapy but is usually manifested three to six months after treatment (Dreizen 1990).

Scarring and thickening of arteriole walls result in a diminished blood supply which may lead to muscle necrosis and fibrosis. Scars that form in muscle bundles and subcutaneous tissues can contract and limit the ability to open the mouth. The severity of the trismus is dependent on the radiation source, the dose and the number of fields radiated (Engelmier and King 1983).

Only a few studies present data on trismus in children. Generally, children who receive high dosage of radiotherapy, directly to the muscles of mastication may develop this problem. Carl and Wood (1980) reported a case who developed trismus as a result of cancer therapy. The patient had an embryonal rhabdomyosarcoma of the left cheek. She was treated surgically by total resection and a modified dissection of the left side of the neck. After surgery, she received 3900 rads to the left area of the cheek and 4000 rads to the neck and mediastinum. She also had a course of chemotherapy consisting of actinomycin D and vincristine.
Trismus seems not to be a problem when the radiation field does not involve those muscles. Welbury et al (1984) found no abnormality of mouth opening in 64 children, aged from three to 20 years who were in long term remission from malignant disease. They did not, however, describe a method of assessing mouth opening. Maguire et al (1987) measured the distance between the incisal edges of upper and lower incisors while study children were asked to open their mouth as wide as possible. They reported no difference in maximal mouth opening between the long-term survivors of childhood leukaemia and their siblings.

2.4.4 Malocclusion

Malocclusion may occur in patients surviving childhood cancer. This problem may be due to altered eruption of teeth or to radiation-induced and/or chemotherapy-induced growth alterations, i.e., jaw and tooth size discrepancies. Jaffe et al (1984) reported abnormal occlusal relationships with relative maxillary retrognathism and/or mandibular prognathism in four patients treated with chemotherapy and radiation to the head and neck, but did not mention malocclusion in the leukaemic group. Welbury et al (1984), however, did not find any variation from normal in occlusion of 64 patients who had received chemotherapy and cranial irradiation.

In 1987, Maguire and others examined 52 long-term survivors of childhood leukaemia or solid tumours, not involving the head and neck. They reported significantly more abnormal occlusion in patients with a solid tumour, compared with patients with leukaemia.

Kaste et al (1994) described two cases of severe malocclusion due to micrognathia. The children had received high dosage radiation (>3000 cGy) for childhood facial tumours before the age of five years.
2.4.5 Dental Maturity

In children treated with chemotherapy for ALL, a temporary reduction of somatic growth has been found during active treatment, whereas normal growth is found three years after the first induction therapy (Herber et al 1985, Clayton et al 1988). This is in contrast to the observations in children treated with chemotherapy in combination with cranial irradiation. In those patients a permanent reduction of somatic growth is found (Wells et al 1983, Robison et al 1985, Kirk et al 1987). This effect of cancer treatment has led to an interest in assessing dental maturity in these patients, although, the results from previous studies have not been conclusive on the effect of cancer therapy on dental age.

In the study of Adatia (1968), only one of 13 patients treated with cyclophosphamide, methotrexate, and vincristine for Burkitt's tumour appeared to have delayed dental development, while 9 of them were normal.

Purdell-Lewis et al (1988) presented the least number of erupted permanent teeth in long-term survivors of childhood cancer treated with chemotherapy compared with the control group. They found that 8 of 45 patients showed a delayed tooth formation. The method for assessing the delayed dental development, however, was not described in any of their studies.

Pajari and others (1988b), using the system for assessing the dental maturity of Demirjian et al (1973), concluded that dental maturity in children cured of cancer differed insignificantly from that of the controls.

Dahllöf et al (1989a) determined the dental maturity of 44 children with haematological malignancies treated with chemotherapy by using the Demirjian and Goldstein (1976) scoring system. They also found no significant difference in dental maturity and eruption of permanent teeth in children treated with chemotherapy compared to healthy controls.
2.4.6 Dental Developmental Abnormalities

2.4.6.1 Radiation effects

According to Desjardins (1930), as early as 1905, only ten years after Wihelm Roentgen discovered X-rays, Recámer and Tribondeau reported the first observation pertaining to the effect of irradiation on the developing dental tissue. They noted under-development of the teeth and skull of a kitten on the side which had been exposed to Roentgen rays.

Many observations and experiments in animals have demonstrated the effects of irradiation on developing dental tissue. Discrepancies exist as to the relative sensitivity of the ectodermally and mesodermally derived odontogenic cells and the relative radiosensitivity of the various stages of cell life. In general, the biologic effects of ionising radiation on the oral structures, including teeth, vary in degree according to type, source and amount of radiation exposure, and the type of living tissue exposed, as well as its stage of development at the time of irradiation. The odontoblasts appear to be more sensitive than the ameloblasts (Burstone-1950). Most authorities classify the early cells of the odontoblastic series prior to beginning to produce dentine, as being the most vulnerable to radiation (Collett and Thonard,1965, Adkins 1967, Saad et al 1991).

These presecretory odontoblasts are proliferating rapidly and have increased mitotic activity (Ten Cate 1989). Mature secretory odontoblasts and ameloblasts are not affected by lower dose radiation. Histologically, irradiated presecretory odontoblasts change from columnar to cuboidal shape. Mitotic activity discontinues, although the cells do not die. "Osteodentine" forms between the arrested odontoblasts and the pulp. The osteodentine is secreted by osteoblast-like cells originating from undifferentiated pulp mesenchyme. The pulp mesenchyme forms these cells either due to direct radiation damage, or due to induction by the damaged odontoblasts (Adkins 1967). The osteodentine is visible microscopically as a "niche" in the dentine, or as a wavy, irregular dentinoenamel junction (Lindvall et al 1972). It is delineated from normal dentine both apically and incisally, designating that only presecretory odontoblasts are damaged by low-dose radiation (Goho 1993).
Osteodentine also differs chemically from normal dentine. In normal dentine, phosphorylated phosphoprotein (PP-H) is the predominant noncollagenous protein. PP-H originates hydroxyapatite nucleation, an early step in dentinogenesis. The prominent reduction of PP-H in osteodentine alters its ability to commence osteogenesis which subsequently results in shortened, thin and tapered roots (Goho 1993).

Low-dose radiation effects noted in enamel appear to be due to damage to the underlying dentine and not to direct ameloblast injury. Nucleation of enamel crystals requires a properly mineralised dentine substrate. Enamel crystals theoretically develop from existing dentine crystals at the dentinoenamel junction. Abnormal osteodentine alters dentinogenesis, therefore the mineralisation of enamel is altered which results in enamel hypoplasia over the defective dentine (Goho 1993). The extent of damage in developing teeth ranges from no demonstrable odontogenic anomaly, except for reduced size, to a complete failure of tooth development (Hiatt et al 1979, Saad et al 1991).

The disturbances usually occur if the total dose is sufficiently large. Degeneration of developing odontoblasts, formation of osteodentine and production of irregularities at the dentine-enamel junction have consistently been described following doses in excess of 1000 cGy of X-radiation (Adkins 1967). A dose as low as 200 cGy has been reported as causing localised dental effects (Lindvall et al 1972). A fraction of the total dose did not significantly reduce the deleterious effects which the single dose had on the development of dentine (Adkins 1967).

Although no experiments on humans can be conducted to study the influence of irradiation on the developmental patterns of bone and teeth, human case reports indicate that exposure of developing dental tissue to therapeutic dosages of radiation is associated with dental maldevelopment (Bruce and Stafne 1950, Gorlin and Meskin 1963, Pietrokovski and Menczel 1966, Weyman 1968, Poyton 1968, Carl and Wood 1980, Dury et al 1984, Goodman and Fuks 1985, Berkowitz et al 1989).
The defects most commonly seen are tooth agenesis, microdontia, altered morphology of the crown, enamel hypoplasia, root shortening and tapering, root agenesis, premature completion of the calcification of the permanent teeth, early and delayed tooth eruption.

In 1984, Jaffe and others evaluated 45 patients receiving maxillofacial radiation for lymphoma, leukaemia, rhabdomyosarcoma and miscellaneous tumours. They detected dental and maxillofacial abnormalities in 82% of these patients. Dental abnormalities comprised foreshortening and blunting of roots, incomplete calcification, premature closure of apices and delayed or arrested tooth development.

The severity of dental malformation is dependent on the stage of development of the dental structures irradiated and the dosage of radiation (Berkowitz et al 1988).

If the radiation preceded the stages of morphodifferentiation and calcification, the tooth bud may be destroyed. Irradiation at a later stage, after calcification has been initiated, may alter cellular differentiation, causing malformation or arrested growth (Goodman and Fuks 1985).

Since immature teeth are at greater risk for developmental disturbance than mature teeth, the child's age at the initiation of irradiation is also an important determinant. In a study by Dahllöf and co-worker (1988), patients who received total body irradiation (1000 cGy) and children younger than 6 years of age at the time of treatment had the most severe and extensive dental aberrations, including impaired root development, enamel hypoplasia and microdontia. Similar results were presented by Sonis et al (1990) who found that the severity of dental developmental abnormalities was greater in children who received irradiation before 5 years of age.

Deleterious effects on undeveloped and developing teeth were observed when dosages as low as 400 cGy were used (Weyman 1968). A dose of 1000 cGy is thought sufficient to permanently damage mature ameloblasts, and 3000 cGy is sufficient to halt tooth
development (Blozis and Robinson 1968). In a comparison study of different cranial irradiation dosages, Sonis et al 1990, found that the patients treated with an irradiation dose of 2400 cGy presented more severe disturbances of dental development than those treated with a dose of 1800 cGy.

2.4.6.2 Chemotherapy effects

The literature has concentrated on the experimental model of giving chemotherapeutic agents to test animals and examining alterations in dental development. In experiments with rats, mice and hamsters, the effects of cyclophosphamide, vinblastin, vincristine, doxorubicin, bleomycin and 5-fluorouracil (5-FU) have been detailed. Rosenberg (1990) summarised the effects observed in several studies as follows:

Histological and histochemical changes were seen in the enamel, dentine, pulp, periodontal ligament and Hertwig's root sheath. Altered enamel formation appeared to be due to irregular enamel matrix formation, impaired secretory function, restricted membrane permeability of ameloblasts, decreased ameloblast reproduction, and inhibition of calcium exchange across the cell membrane to the enamel matrix. Calcium transport within the ameloblast was not apparently inhibited. These changes resulted in enamel opacities, surface irregularities, and acquired amelogenesis imperfecta.

Dentinal changes appeared to be due to impaired microtubule secretory function, which resulted in the formation of an irregular dentine matrix with unusual collagen aggregations. The polarity of odontoblast nuclei, as well as the number of cytoplasmic organelles, was lost. Increased intercellular spacing, reduced contact surfaces in desmosomes, and restricted membrane permeability were also observed. The clinical significance of these odontoblastic changes included shortening, thinning and blunting of the tooth roots. The pulp became hypocellular and thus prone to easier necrosis in the face of rampant caries. The destruction of Hertwig's root sheath, and animal cell culture studies of periodontal ligament collagen interaction with dentine, support the findings of rootless teeth still having the capacity to erupt without complete root formation.
According to Goho (1993), chemotherapy injures presecretory odontoblasts, creating dentine niches identical to those caused by radiation. Because of the short life of chemotherapeutic agents, dental defects are usually localised. This results from temporary changes in odontoblast function, instead of odontoblast death. Narrow pulp chambers and localised enamel defects may be noted at the level of dentine niche. Coronal size and shape are not affected, however, since crown morphology is determined before birth. Niche formation at or below the level of the cementoenamel junction results in shortened, thin roots. Repetitive high doses of some agents, such as cyclophosphamide, may result in root agenesis. Intensive, repetitive chemotherapy at the time of initial hard tissue formation may cause tooth agenesis.

Some chemotherapeutic agents also affect mature secretory odontoblasts and ameloblasts. Vinblastine and vincristine disrupt the cytoplasmic tubules of intercellular transport system. Interference with odontoblast microtubules disrupts collagen fibril formation and dentine matrix secreting resulting in short, thin and tapered roots. Disruption of the ameloblast microtubule calcium transport mechanism results in hypomineralised enamel defects. Ameloblast microtubules also form the ruffled border where absorption of organic material from the enamel matrix occurs. Vinca alkaloids destroy the ruffled border and create smooth-ended ameloblasts which cannot remove organic proteins from enamel matrix. Hypomature enamel defects result (Goho 1993).

In contrast to the studies in animals, a small number of studies have investigated the effects of chemotherapeutic agents on human dental development. In the first study carried out by Jaffe et al (1984), possible chemotherapeutic effects were found in five of 23 patients who received treatment for tumours outside the head and neck region. These effects of chemotherapy consisted of acquired amelogenesis imperfecta, microodontia of bicuspid teeth, and a tendency toward thinning of roots with an enlarged pulp chamber.

Macleod et al (1987) conducted a histological study of twenty-one teeth from nine patients who had received cytotoxic chemotherapy for malignant disease. They reported
the increased prominence of incremental lines in the dentine with their number and
distribution corresponding to periods of intravenous therapy and to the specific agent,
vincristine. The findings suggested a temporary disturbance of microtubular function in
odontoblasts which resulted in decreased secretion of collagenous dentine matrix.
Calcification, however, appeared to be unaffected.

In the same year, Rosenberg et al (1987) performed both qualitative and quantitative
analysis on seventeen long-term survivors of ALL treated with only combination
chemotherapy at between four and ten years of age. All were assessed after reaching age
12. Shortening, thinning and blunting of roots and their apices were reported.
Specifically, five of the seventeen have marked shortening and 13 of seventeen have
marked thinning of the root subjectively on periapical radiographs. A 63% to 84%
reduction of premolar root length in study patients was disclosed when compared with
the mean of the historical controls.

2.4.6.3 Combined effects of radiotherapy and chemotherapy
The literature has also concentrated on the chronic dental complications in patients who
had received both chemotherapy and irradiation to the head and neck region. The
leukaemic patients are frequently the main study population as they are a major childhood
cancer with the highest survival rate. The fact that the standard treatment of leukaemia
usually comprised both combination chemotherapy and cranial irradiation leads to a
difficulty in determining the cause of dental developmental defects in these patients.
Many authors have assumed that only chemotherapy has influenced these patients
because the field of radiation did not cover dental arches and/or the salivary glands
The effect of scattered radiation cannot, however, be overlooked.

A study of 64 children (37 with leukaemia and 27 with solid tumours) who received
chemotherapy and cranial irradiation showed the increased incidence of hypodontia and
hypoplastic teeth compared with the general population (Welbury et al 1984). There
was, however, no difference in these defects between the patients with leukaemia and with solid tumours. The results implied that cranial irradiation may not influence the incidence of abnormalities. The higher incidence of developmental defects could only be explained in part by the effects of chemotherapy or the disease itself. Many of the abnormalities must have occurred outside the treatment period. In animals there was a variable response of the teeth to chemotherapy (Vahlsing et al 1977), and it is likely that a similar variability would occur in humans.

Maguire et al (1987) reported several dental abnormalities including failure of tooth development, small crowns, crown hypoplasia and abnormal root development in 65% of children surviving malignant disease.

Pajari et al (1988b) measured the root area from panoramic radiograph by computer linked planimetry and found that the mean root area in children with cancer was reduced but the crowns were not affected.

Pajari and others (1988c) described enamel opacities in all 37 children after anti-neoplastic therapy. The leukaemia patients had opacities in all dentitions, while the other cancer patients showed alterations only of the permanent teeth. The prophylactic cranial irradiation in leukaemia patients probably influenced the result of this study.

Purdell-Lewis et al (1988) showed evidence of disturbed amelogenesis in 43 of 45 long term survivors of childhood malignancies. This resulted in aesthetically displeasing grooves, pits and discolouration. Twenty-three children were counselled on the possibility of cosmetic dentistry. They also mentioned other developmental abnormalities which included malformed roots, shortened roots and smaller crowns. They did not, however, provide any data on the incidence of these anomalies.

In the north of England, Nunn and co-workers (1991) assessed 52 children in remission from childhood cancer, and 41 siblings, for dental anomalies. All the treated children had
received chemotherapy. The leukaemic patients also had received radiotherapy, but not to the jaws. Significantly more dental anomalies were detected radiographically in the treated group (46%, 24 of the 52 patients).

Fromm et al (1986) evaluated 20 children who had received chemoradiotherapy for soft tissue sarcomas of head and neck. They found eleven of them showed root foreshortening or agenesis of developing teeth and nine had crown defects.

In Sweden, Dahllöf and others (1988) observed 16 bone marrow transplant (BMT) recipients who received chemotherapy and total-body irradiation. All 16 patients had impaired root development, with short V-shaped roots, five exhibited complete failure of root development with premature apical closure, and four had enamel hypoplasia. Similar disturbances were found in both maxillary and mandibular teeth. Microdontia was found in patients younger than 5.4 years of age at BMT but did not affect all teeth at the same level of development. This may be due to the differences in susceptibility of individual teeth in the same patient.

Berkowitz et al (1989) reported a child with multiple dental anomalies including agenesis, ectopia, crown and root malformation after surviving a rhabdomyosarcoma of the left buccinator. This case was interesting because he had an unaffected identical twin for comparative study.

Recent studies have associated dental disturbances found in survivors of childhood cancer with their age at the initiation of treatment and to different forms of antineoplastic therapy. In 1988, Dahllöf and others concluded that patients younger than 6 years of age at BMT exhibited the most severe and extensive dental aberrations.

Sonis et al (1990) determined dental abnormalities from panoramic radiographs of survivors of ALL. They reported that 94% of all patients (97) and 100% of patients younger than five years of age at diagnosis developed dental abnormalities including
tooth agenesis, arrested root formation, microdontia, and enamel hypoplasia.

Nasman et al (1994) showed equal numbers of teeth affected by disturbances in enamel mineralisation in the total body irradiation and chemotherapy group which was significantly higher than healthy controls. From panoramic radiograph assessment, they also found that children treated with total body irradiation exhibited an increased mean number (15.9) of teeth with disturbances in root development compared with that (1.2) of the chemotherapy group.
CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY POPULATION

From 1989-1994, two hundred and one long-term survivors of childhood cancer who had received treatment before the age of 13 years, and remained in continuous remission, were examined at the Late Effects Clinic at the Children's Hospital, Camperdown, Sydney. All patients were evaluated by a multidisciplinary team.

The patient's history was obtained from his/her medical record which includes the following details:

- Name
- Date of birth
- Gender
- Diagnosis
- Age at diagnosis
- Age at the initiation of treatment
- Oncology treatment protocols which included site of surgery, field of radiation, chemotherapeutic protocol or agents, and treatment duration.
- Medical complications
3.2 ASSESSMENTS

Dental examination comprised clinical examination of the soft and hard tissue and a panoramic radiograph. The patients were examined with mirror and probe under the ambient light. The following definitions were used for assessment.

3.2.1 Extraoral Examination

3.2.1.1 Facial appearance

Normal

The facial appearance was considered normal, if:
- it was bilaterally symmetrical, showing a similarity of the external contour of the right and left sides of the upper and lower face (Proffit et al 1993).
- it had no marked deformity of any part of the face.

Deformity

The patient's face was subjectively defined deformed when it showed marked asymmetry, or deformity of any part of the face. **Figure 3-1** demonstrates an example of patient with facial deformity.

3.2.1.2 Jaw function

Normal

The function of the jaw was defined as normal if the mandible was able to move normally without any signs of temporomandibular joint dysfunction, such as joint pain, crepitus or limitation of opening.

**Trismus** (Limitation of Jaw Opening)

This impairment was indicated if the vertical distance between the incisal edge of the upper central incisor and the incisal edge of the opposed lower incisor was less than 40 millimetres when the maximal opening was performed (Ingervall 1970, Agerberg 1974, Solberg et al 1979).
Figure 3-1  A patient with facial deformity
3.2.2 Intraoral Examination

3.2.2.1 Periodontal status

Normal
The periodontal status was defined as normal when:

1. the gingivae were pink or coral pink in colour, stippled and had a thin knife-edged gingival margin,
2. the interdental papillae filled the interproximal space,
3. the attached gingivae had a firm and resilient consistency,
4. there was no gingival bleeding and pathologic tooth mobility (Carranza 1990).

Gingivitis
Gingivitis is the inflammation of the gingival unit. Inflammation was indicated by clinical signs such as redness, oedema, swelling and bleeding on gentle probing (Carranza 1990).

Periodontitis
Periodontitis was indicated by the evidence of loss of connective tissue attachment from the root surface, resulting in pocket formation and pathologic tooth mobility (Carranza 1990).

3.2.2.2 Occlusion

Normal occlusion
Normal occlusion was described by the normal molar relationship and the regular arrangement of the teeth in the line of occlusion. Normal (Class I) molar relationship occurs when the mesiobuccal cusp of the upper first permanent molar occludes in the mesiobuccal groove of the lower first permanent molar (Proffit et al 1993).

Class I malocclusion
Class I malocclusion was defined by the normal (Class I) molar relationship with an irregularity in arrangement of teeth in the line of occlusion (Proffit et al 1993).

Class II malocclusion
Class II malocclusion was determined if the lower first permanent molar was distally positioned relative to the upper first permanent molar. The line of occlusion may or may not be correct (Proffit et al 1993).
Class III malocclusion
Class III malocclusion is defined by the lower first permanent molar being mesially positioned relative to the upper first permanent molar. As for the Class II malocclusion, the line of occlusion was not specified (Proffit et al 1993).

3.2.2.3 Need for orthodontic treatment

Not required
The patients were determined not to need orthodontic treatment when they had normal occlusion and slight anomalies. For example one or more rotated or tilted teeth, slight crowding, or spacing which disturbed the regular alignment of the teeth (Code 0 and 1 in WHO 1987).

Required
The patients were generally described as needing orthodontic treatment when the anomalies caused an unacceptable effect on facial appearance, or a significant reduction in masticatory function or impairment of speech. The presence of one or more of the following conditions of the four anterior incisors were included:
- maxillary overjet estimated to be 9 mm. or more;
- mandibular overjet, anterior crossbite equal to or greater than a full tooth depth;
- openbite;
- midline shift estimated to be more than 4 mm.; and
- crowding or spacing estimated to be more than 4 mm. (Code 2 in WHO 1987).
In addition, the patients who had received orthodontic treatment were included in this category.
3.2.2.4 Caries status
The number of decayed, missing due to caries, and filled teeth were recorded. The index dmft described the caries status of the primary teeth while the DMFT described the permanent teeth. Using a modification of the five levels of dental caries severity for the age 12 Years (World Statistical Quarterly 1987), the patients' caries status were classified into 4 groups:

- **Caries free**: dmft or DMFT = 0
- **Mild**: dmft or DMFT ≤ 3
- **Moderate**: dmft or DMFT > 3 but ≤ 6
- **Extensive**: dmft or DMFT > 6

3.2.3 Radiographic Examination
Assessment of panoramic radiographs was performed by the writer to evaluate dental maturity and dental developmental disturbances.

3.2.3.1 Dental maturity
Dental maturity was analysed using the system of Demirjian and Goldstein (1976). According to this system, the dental age of each patient was estimated by reference to the radiological appearance of the seven teeth on the left side of the mandible in a panoramic radiograph. As described in Appendix II, eight stages were defined from the first appearance of calcified points of the tooth to the closure of the apex. The summed scores for all seven teeth give a dental maturity score which can be converted into a dental age. In the case of missing teeth, the contralateral teeth were used.

In this study only 116 of 201 patients were recruited for dental age assessment. The following groups of patients were excluded:
- the female patients who were older than 15.7 years of age at the time of radiographic examination,
- the male patients who were older than 16.0 years of age at the time of radiographic examination,
These two groups were excluded because a dental maturity score is constant beyond those ages, according to Demirjian et al (1973), and
- the patients who had a congenital absence of one of the seven teeth in all four quadrants.

3.2.3.2 Developmental disturbances of tooth formation

Both clinical and radiographic examination were used to assess the developmental disturbances of the teeth. The clinical examinations were recorded and correlated with an alteration of crown form and root form revealed by the panoramic radiographs. For example crown disturbances include microdontia, conical-shape, congenital oligodontia, whilst root disturbances include shortening, tapering, dilaceration and root agenesis.

Definition of developmental disturbances of tooth formation

Microdontia refers to the tooth which is smaller than normal, i.e., outside the usual limits of variation (Stewart et al 1982). It also includes the conical-shaped crown form frequently seen in lateral incisors.

Congenital tooth agenesis means the absence of tooth/teeth in the primary and/or the permanent dentition noted during both clinical and radiographic examination without a history of extraction.

Shortening of the root refers to a root which is shorter than normal length but has normal shape.

Tapering or narrowing of the root refers to a root which has thin dentinal wall and/or has a root apex ending in a sharp thin point (Rosenberg et al 1987).

Root agenesis refers to the arrested root formation measured from the cementoenamel junction. Root which was measured as being shorter than one third of the crown height was also included in this category.

The teeth with incompletely formed roots were not included in the assessment for the disturbances in root formation. They were classified as undetermined teeth if they did not exhibit any other anomalies.
Grading of severity of dental developmental disturbance

Each tooth was subjectively assessed for the severity of dental developmental disturbance by using the following guidelines:

Normal  Normal in size, colour, structure and shape of both crown and root

Mild

Crown:  - Microdontia with recognisable morphology (Figure 3-2)

Root:  - Shortening or tapering of root with the root length equal to or not greater than the crown length. The assessment was carried out using the measurements of Woelfel (1990) as shown in Appendix III.

- Dilaceration, taurodontia, abnormal number of roots, pulp stones.

Severe

Crown:  - Microdontia with unrecognisable characteristics (Figure 3-3),

- Congenital tooth agenesis

Root:  - Shortening or tapering of the root with the root length less than the crown length. The assessment was carried out by using the same table of measurement as described above for the mild group.

- Root agenesis

An impression of the overall severity in each patient was categorised into the following four arbitrary groups by considering the effects on the development of all teeth (except the third permanent molars).

Normal

The patient had normal formation of both the crown and root of every tooth, except the third permanent molars. Figure 3-4 illustrates an example of patient with normal dentition.
Mild

The patient was rated mildly affected when there was
- only mild disturbances of crown and/or root or
- any severe disturbance affected only 1-2 teeth and other teeth being normal.

Figure 3-5 shows an example of patient, presenting mild disturbance of dental development.

Moderate

The patient was categorised moderately affected if mild and/or severe disturbances of the crown and/or root were obtained but the severe disturbances did not involve more than seven teeth (25% of total number of permanent dentition when excluding the third molars).

Some examples of patients who were determined to have moderate dental defects are exhibited in Figure 3-6 and Figure 3-7.

Severe

The patient was graded severely affected if mild and/or severe disturbances of the crown and/or root formation were evident and the severe disturbances involved more than seven teeth. Figure 3-8 and Figure 3-9 are examples of patients who were evaluated to be severely affected.

Undetermined

The patient in this group was one whose permanent dentition had normal number and crown shape but the roots had incompletely formed. The evidence, available at the time of examination, was inadequate to classify him or her into any of the previous categories.
3.3 STATISTICAL ANALYSIS

The data from medical history, clinical examination, and radiographic assessment were directly entered into a microcomputer. The variables included name, medical record number, sex, date of birth, diagnosis, date and age at diagnosis, radiation site and dose, chemotherapeutic protocol and duration, date and age at dental examination, medical complications, and the dental assessments.

The statistical analysis was carried out by the SPSS/PC+ statistical package. The differences were considered to be highly significant if p-value < 0.001, p-value significant if p-value < 0.01 and if p-value < 0.05.

According to Shaw and Murray (1975), the intra-examiner reproducibility ratio was calculated from the formula:

\[ r = \frac{a}{b} \quad \text{where} \quad a = \text{number of teeth with disagreement in the diagnosis} \]
\[ b = \text{number of teeth with a consistent diagnosis} \]

Percent agreement was computed to measure the intra-examiner reproducibility.

\[ P = \frac{b}{(a + b)} \times 100 \]

In this study \( r = 0.08 \) and \( P = 92.6 \% \)
Figure 3-2  Recognisable microdontia

Figure 3-3  Unrecognisable microdontia
Figure 3-4  Normal dental development

Figure 3-5  Mild disturbance of dental development
Figure 3-6  Moderate disturbance of dental development

Figure 3-7  Moderate disturbance of dental development
Figure 3-8  Severe disturbance of dental development (A), compared with the patient's identical twin (B)
Figure 3-9  Severe disturbance of dental development
CHAPTER FOUR

RESULTS

4.1 CHARACTERISTICS OF THE STUDY POPULATION

The gender, diagnosis, age at diagnosis, age at examination, and the time interval from the completion of cancer therapy to the present dental examination are presented in Table 4-1.

4.1.1 Gender

As shown on Table 4-1, males are more affected from cancer than females in the ratio of 1.4:1.

4.1.2 Diagnoses

Table 4-1 and Figure 4-1 show that the major cancer disease is acute leukaemia (54.2%). This comprises of acute lymphoblastic leukaemia (n=105) and acute myelocytic leukaemia (n=4). The remaining diagnoses are rhabdomyosarcoma (10.0%), Wilms' tumour (9.0%), Non-Hodgkin's lymphoma (8.0%), neuroblastoma (7.0%), and other cancers (11.9%). The diagnosis of other cancers consists of adrenocortical carcinoma (n=1), Ewing's tumour (n=4), germ cell tumours (n=6), histiocytosis-X (n=1), Hodgkin's disease (n=4), malignant fibromatosis (n=1), medulloblastoma (n=1), retinoblastoma (n=5), and small cell tumour (n=1).

4.1.3 Mean Age at Diagnosis

The mean age at diagnosis of this population is 4.8 years with standard deviation of 3.1 years (4.8±3.1 years), ranging from 0.1 to 13.0 years. The neuroblastoma has the youngest mean age at diagnosis (1.7±1.2 years), ranging from 0.5 to 5.8 years. The mean age at diagnosis of Wilms' tumour is 3.9±2.2 years, ranging from 1.0 to 8.6 years. The mean age at diagnosis of acute leukaemia is 4.6±2.5 years, ranging from 0.8 to 13.0 years. The mean age at diagnosis of other cancers is 5.6±4.5 years, ranging from 0.1 to
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12.8 years. The mean age at diagnosis of rhabdomyosarcoma is 6.0±4.5 years, ranging from 1.2 to 11.5 years. Non-Hodgkin's lymphoma has the oldest mean age at diagnosis (7.2±3.4 years), ranging from 3.0 to 13.0 years.

4.1.4 Mean Age at Dental Examination

The mean age for dental examination of this population is 15.2±4.4 years, ranging from 5.0 to 32.3 years. Neuroblastoma has the youngest mean age at dental examination (12.8±1.2 years), ranging from 7.7 to 32.2 years. Mean age at dental examination of Wilms' tumour is 13.3±3.1 years, ranging from 8.6 to 20.8 years. Mean age at dental examination of acute leukaemia is 15.0±3.9 years, ranging from 8.8 to 26.8 years. Mean age at dental examination of other cancers is 15.7±5.4 years, ranging from 5.0 to 26.0 years. Mean age at dental examination of rhabdomyosarcoma is 17.1±4.1 years, ranging from 10.9 to 24.7 years. Non-Hodgkin's lymphoma has the oldest mean age at dental examination (18.2±4.2 years), ranging from 10.5 to 25.7 years.

4.1.5 Category of the Study Population

As displayed in Table 4-2, the patients recruited in this study are categorised into three groups:

Cranial irradiation group, including all patients who received cranial irradiation with or without chemotherapy,

Head and neck irradiation group, including all patients who received radiotherapy of head and neck, except the cranium, and who received total body irradiation, with or without chemotherapy, and

Chemotherapy group, comprising all patients who received chemotherapy only including those receiving chemotherapy with irradiation not involving head and neck regions.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Gender</th>
<th>Age at diagnosis (years)</th>
<th>Age at examination (years)</th>
<th>Time (years) from initiation of cancer treatment to examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>M/F</td>
</tr>
<tr>
<td>Acute Leukaemias</td>
<td></td>
<td>109</td>
<td>54.2</td>
<td>64/45</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td></td>
<td>20</td>
<td>10.0</td>
<td>15/5</td>
</tr>
<tr>
<td>Wilms' tumour</td>
<td></td>
<td>18</td>
<td>9.0</td>
<td>9/9</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td></td>
<td>16</td>
<td>8.0</td>
<td>11/5</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td></td>
<td>14</td>
<td>7.0</td>
<td>9/5</td>
</tr>
<tr>
<td>Other cancers</td>
<td></td>
<td>24</td>
<td>11.9</td>
<td>9/15</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>201</td>
<td>100.0</td>
<td>117/84</td>
</tr>
</tbody>
</table>
Table 4-2  Characteristics of patients in three different treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Gender</th>
<th>Age at diagnosis (years)</th>
<th>Age at examination (years)</th>
<th>Time (years) from initiation of cancer treatment to examination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>M/F</td>
<td>Mean</td>
</tr>
<tr>
<td>Cranial irradiation</td>
<td>114</td>
<td>56.7</td>
<td>67/47</td>
<td>1.4:1</td>
</tr>
<tr>
<td>Head &amp; neck irradiation</td>
<td>29</td>
<td>14.4</td>
<td>15/14</td>
<td>1.1:1</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>58</td>
<td>28.9</td>
<td>35/23</td>
<td>1.5:1</td>
</tr>
<tr>
<td>Total</td>
<td>201</td>
<td>100.0</td>
<td>117/84</td>
<td>1.4:1</td>
</tr>
</tbody>
</table>
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Figure 4-1  Percentage of patients by Diagnosis

Figure 4-2  Number of patients by Dosage of cranial irradiation

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**Figure 4-3** Number of patients by Dosage of head and neck irradiation

![Bar chart showing the number of patients by dosage of head and neck irradiation. The x-axis represents various dosage levels (1000, 1600, 2400, 3200, 3400, 3500, 3600, 3800, 4000, 4500, 5000, 5400, 5800, 6000, 6200, 6800, 6900, 9500, 9700, 9900, 10100, 10200, 10300). The y-axis represents the number of patients ranging from 0 to 5.]

**Table 4-3** Duration of cancer treatment, based on the time course of chemotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (Yrs)</th>
<th>Median (Yrs)</th>
<th>SD</th>
<th>Range (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial irradiation</td>
<td>2.9</td>
<td>3.0</td>
<td>0.9</td>
<td>1.0-7.0</td>
</tr>
<tr>
<td>Head and neck irradiation</td>
<td>2.0</td>
<td>2.0</td>
<td>0.9</td>
<td>0.6-5.0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1.8</td>
<td>2.0</td>
<td>0.7</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>2.0</td>
<td>1.0</td>
<td>0.3-7.0</td>
</tr>
</tbody>
</table>
4.1.5.1 Cranial irradiation group

The patients in this group totalled 56.7% (n=114) of the study population. Males are more affected from cancer than females in a ratio 1.4:1 (Table 4-2). Mean age at diagnosis of this group is 4.8 years, ranging from 0.8 to 13.0 years. Mean age at examination is 15.1±3.7 years, ranging from 8.8 to 26.8 years.

Ninety seven patients (85.1%) in this group were diagnosed with acute lymphoblastic leukaemia. The next most prevalent diagnosis is Non-Hodgkin's lymphoma (n=10, 8.8%), followed by acute myelocytic leukaemia (n=5, 4.4%), neuroblastoma (n=1, 0.9%), and medulloblastoma (n=1, 0.9%).

As shown in Table 4-3, the mean duration of treatment in the group is 2.9±0.9 years, ranging from 1.0 to 7.0 years. A significant difference between mean duration of treatment of the three groups was detected by one way ANOVA analysis with F ratio =32.66 and p<0.0001. Multiple comparison, using Scheffe technique, reveals a significant difference in mean duration of treatment in the cranial irradiation group, compared with the head and neck irradiation and the chemotherapy groups. There is, however, no difference in duration of cancer treatment between these latter two groups.

The mean dosage of cranial irradiation is 2242 cGy. The dosage of irradiation ranges from 1600-cGy to 8500-cGy. The main dosages used in most of these patients were either 2400-cGy (57%) or 1800-cGy (36%). Figure 4-2 shows the number of patients receiving varying dosages of cranial irradiation.

The LSA₂L₂ and BFM protocols are the main chemotherapeutic protocols. Sixty patients (52.6%) received LSA₂L₂ and 30 patients (26.3%) received BFM. Twenty of the patients in this group (17.5%) received other chemotherapeutic protocols, including ACCSG, ACCSGV, ANZCCSG, CHOP, DZAPO, Pinkel, and various multiagent regimens. There are 4 patients in this group (3.5%) cured by using two different chemotherapeutic protocols.
4.1.5.2  Head and neck irradiation group

This group involves 14.4% (n=29) of the total population. Males are slightly more affected from cancer than females in a ratio 1.1:1. The mean age at diagnosis for this group is 5.4±3.5 years, ranging from 0.5 to 13.0 years. The mean age at examination is 16.2±4.7 years, ranging from 5.0 to 23.6 years (Table 4-2).

The various diagnoses of patients in this group include 9 (31.0%) patients with rhabdomyosarcoma, 5 (17.2%) with acute lymphoblastic leukaemia, 5 (17.2%) with retinoblastoma, 4 (13.8%) with Hodgkin disease, and 4 (13.8%) with Non-Hodgkin lymphoma.

The mean duration of treatment in this group is 2.0±0.9 years, ranging from 0.6 to 5.0 years (Table 4-2).

The dosage of head and neck irradiation varies widely ranging from 1000 cGy to 9500 cGy. However, the mean value of 4355 cGy is higher than that for the cranial irradiation group. It's median is 4250 cGy. In contrast to the cranial irradiation group, children in this group are unlikely to receive a major dosage of irradiation. Figure 4-3 illustrates the numbers of patients and their differing dosages of head and neck irradiation.

Chemotherapeutic protocols used in this group vary widely. Seven patients (24.1%) were treated by a multiagent protocol, comprising actinomycin, adriamycin, cyclophosphamide, and vincristine. Three patients (10.3%) received LSA1L2 treatment protocol with total body irradiation and three patients (10.3%) were cured by the ACOPP protocol: Four patients (13.8%) received 2 chemotherapeutic protocols whilst 11 patients (38.0%) had other different treatment protocols. One patient did not have any chemotherapy.
4.1.5.3 Chemotherapy group

This group involves 28.9% (n=58) of the study population. Males are more affected by cancer than females in ratio 1.5:1. The mean age at diagnosis for this group is 4.6±3.5 years, with a range from 0.1 to 11.8 years. The mean age at examination is 15.2±5.3 years, with a range from 7.0 to 32.2 years. The major diagnostic category for patients in this group is Wilms' tumours (n=18, 31.0%), followed by neuroblastoma (n=12, 20.7%), acute lymphoblastic leukaemia (n=2, 3.4%), Non-Hodgkin lymphoma (n=2, 3.4%), Ewing's tumour (n=4, 6.8%), germ cell tumours (n=6, 10.3%), histiocytosis-X (n=1, 1.7%), malignant fibromatosis (n=1, 1.7%), and, finally, small cell tumour (n=1, 1.7%).

The mean duration of treatment for this group is 1.8±0.7 years, ranging from 0.3 to 4.0 years (Table 4-3).

None of the patients in this group had received radiotherapy to the head and neck region. In fact twenty-three patients (39.6%) did not have any radiation therapy at all. The other 35 patients had radiotherapy to other parts of their body including mediastinum, thorax, abdomen, kidney, spine, pelvis, testes, and leg. The radiation doses vary from 1500 to 5000 cGy.

The chemotherapeutic protocols used in this group also vary widely. Seventeen patients (29.3%) were treated by a multiagent protocol, comprising actinomycin, adriamycin, cyclophosphamide, and vincristine. Eleven (19.0%) had a three-drug regimen, consisting of actinomycin, adriamycin, and vincristine and six (10.3%) were cured by actinomycin and vincristine. As well, five patients (8.6%) received adriamycin, cyclophosphamide, dacarbazine, and vincristine whilst four patients (6.9%) had cyclophosphamide and vincristine. The remaining 16 patients (25.9%) received other protocols.
4.1.6 Time from the Initiation of Cancer Treatment to Examination
(Survival Time)

The dental assessments were performed after the median/mean time from the initiation (diagnostic time) of cancer therapy to examination of 9.9/10.4 years with standard deviation of 2.8 years. A range varies from 4.2 to 30.7 years (Table 4-2). As presented in Table 4-2, the mean time from the initiation of cancer treatment to examination for the three groups is similar. For the cranial irradiation group, it is 10.4±2.8 years, 10.6±3.4 years for the head and neck irradiation group, and 10.4±3.8 years for the chemotherapy group. The chemotherapy group presents the widest range for survival time from 6.1 to 30.7 years. This is followed by the cranial irradiation group, ranging from 4.6 to 19.8 years and, finally, the head and neck irradiation group with a range of survival time from 14.2 to 18.2 years.
4.2 ORAL HEALTH

4.2.1 Dental Caries
As presented in Table 4-4, 29.4% of the total patients are caries free, whilst 29.9% show 1-3 carious teeth. The number of patients with 3 to 6 carious teeth is 21.9% and 18.9% of patients have more than 6 carious teeth. The mean DMFT was not obtained but this result suggests that most of the population have a low caries level (0-3 dmft, DMFT).

When dividing the population into three groups, it is found that only the caries patterns of the cranial irradiation and the head and neck irradiation groups are similar to that of the total population in which most of the patients show a low caries level (0-3 dmft, DMFT). Of the cranial irradiation group, 31.6% are caries free, 33.3% show 1-3 carious teeth, 19.3% present more than 3 to 6 carious teeth, and 15.8% have more than 6 carious teeth. Of the chemotherapy group, 32.8% are caries free, 29.3% show 1-3 carious teeth, 20.7% present more than 3 to 6 carious teeth, and 17.2% have more than 6 carious teeth.

In contrast, most of the head and neck irradiation group have a high caries level (>3 DMFT). Only 13.8% of them are caries free, 17.2% show 1-3 carious teeth, 34.5% present more than 3 to 6 carious teeth, and 34.5% have more than 6 carious teeth. Chi-squared analysis, however, reveals no significant difference in caries level among these three diagnostic groups, with $\chi^2 = 11.7$ and $p = 0.069$.

4.2.2 Periodontal Status
As shown in Table 4-5, 29.4% of the total patients have a healthy periodontium, 66.6% have gingivitis and only 4% have periodontitis. The distribution pattern of the periodontal status is also found in the three groups. For the cranial irradiation group, 29.8% have a healthy periodontium, 67.5% have gingivitis, and only 2.6% have periodontitis. Of the head and neck irradiation group, 20.7% have a healthy periodontium, 65.5% have gingivitis, and 13.7% present with periodontitis. Of the chemotherapy alone group,
32.8% are normal, 65.5% have gingivitis, and only 1.7% have periodontitis. Chi-squared analysis shows no significant difference in periodontal status between these three groups, with $\chi^2 = 9.2$ and $p = 0.054$.

**Table 4-4** Dental caries level

<table>
<thead>
<tr>
<th>Caries level</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>36</td>
<td>31.6</td>
<td>4</td>
<td>13.8</td>
</tr>
<tr>
<td>1</td>
<td>38</td>
<td>33.3</td>
<td>5</td>
<td>17.2</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>19.3</td>
<td>10</td>
<td>34.5</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>15.8</td>
<td>10</td>
<td>34.5</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100.0</td>
<td>29</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$\chi^2 = 11.7$, $p = 0.069$

**Table 4-5** Periodontal status

<table>
<thead>
<tr>
<th>Periodontal status</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>34</td>
<td>29.8</td>
<td>6</td>
<td>20.7</td>
</tr>
<tr>
<td>Gingivitis</td>
<td>77</td>
<td>67.5</td>
<td>19</td>
<td>65.5</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>3</td>
<td>2.6</td>
<td>4</td>
<td>13.7</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100.0</td>
<td>29</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$\chi^2 = 9.2$, $p = 0.054$
4.3 FACIAL DEFORMITY

As shown in Table 4-6, only 10.4% of the whole study population present with facial deformity.

When comparing the three groups, the patients treated with head and neck irradiation have a significantly greater incidence of facial deformity than the other two groups ($\chi^2 = 51.9$, $p < 0.0001$). Of the head and neck irradiation group, 48.3% exhibit obvious facial deformity. Only 3.5% of the cranial irradiation group and 5.2% of the chemotherapy group have a facial deformity.

Focusing on the head and neck irradiation group, 24 of them were 9 years old or younger at diagnosis. Thirteen patients (54%) in this age group present with facial deformity. They received various radiation doses, ranging from 3900 cGy to 9500 cGy. Mean radiation dose is 5421 cGy.

Twelve of the 15 patients with no facial deformity were 9 years old or younger at diagnosis. The mean radiation dose is 2270 cGy, varying from 1000 cGy to 6200 cGy. The remaining three patients were 10.7, 10.9 and 12.8 years old at the beginning of treatment and received radiation doses of 3240, 3600 and 5800 cGy, respectively.

Table 4-7 presents details of each patient who has facial deformity. Except for 2 patients in the cranial irradiation group and 3 in the chemotherapy group, all patients presenting with facial deformity underwent procedures involving head and neck surgery.

In the cranial irradiation group, age at commencement of treatment ranges from 3.2 to 11.4 years. Three of the 4 patients received 2400-cGy of cranial irradiation and one had 1800-cGy.
Almost all of the patients (13 of 14) in the head and neck irradiation group had treatment at the age of nine years or younger. All of them received unilaterally high-dose radiotherapy (more than 3000 cGy) to the face and neck regions. More than half (8 of 14) of the patients had been treated for rhabdomyosarcoma.

In the chemotherapy group, all three patients are survivors of childhood Wilms' tumour and received cancer therapy at a young age (up to 5 years old). Adverse effect of chemotherapy is suspected. Radiotherapy should not be associated with facial deformity since the radiation fields did not involve any part of the head and neck. In addition, one patient had no radiotherapy at all.

<table>
<thead>
<tr>
<th>Facial appearance</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>110  96.5</td>
<td>15  51.7</td>
<td>55  94.8</td>
<td>180   89.6</td>
</tr>
<tr>
<td>Deformity</td>
<td>4  3.5</td>
<td>14  48.3</td>
<td>3  5.2</td>
<td>21    10.4</td>
</tr>
<tr>
<td>Total</td>
<td>114  100.0</td>
<td>29  100.0</td>
<td>58  100.0</td>
<td>201   100.0</td>
</tr>
</tbody>
</table>

χ² = 51.9, p < 0.0001
## Results

**Table 4-7** Details of patients with facial deformity

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
<th>Age at diagnosis (years)</th>
<th>Head &amp; neck surgery</th>
<th>Radiation field</th>
<th>Radiation dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial irradiation</td>
<td>ALL</td>
<td>3.2</td>
<td>No</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>4.3</td>
<td>Yes</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>10.0</td>
<td>No</td>
<td>Cranium</td>
<td>1800</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>11.4</td>
<td>Yes</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td>Head and neck</td>
<td>Carcinoma</td>
<td>0.8</td>
<td>Yes</td>
<td>Cranium &amp; parotid gland</td>
<td>4500</td>
</tr>
<tr>
<td>irradiation</td>
<td>NHL</td>
<td>3.0</td>
<td>Yes</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>13.0</td>
<td>Yes</td>
<td>Right neck &amp; pharynx</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>RB</td>
<td>1.3</td>
<td>Yes</td>
<td>Left eye</td>
<td>3900</td>
</tr>
<tr>
<td></td>
<td>RB</td>
<td>2.2</td>
<td>Yes</td>
<td>Left eye</td>
<td>4500</td>
</tr>
<tr>
<td></td>
<td>RB</td>
<td>2.6</td>
<td>Yes</td>
<td>Right orbit</td>
<td>4500</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>2.3</td>
<td>Yes</td>
<td>Right orbit</td>
<td>4000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>2.9</td>
<td>Yes</td>
<td>Left cheek</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>4.9</td>
<td>Yes</td>
<td>Mandible</td>
<td>6000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>5.4</td>
<td>Yes</td>
<td>Left orbit</td>
<td>9100</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>5.9</td>
<td>Yes</td>
<td>Left cheek</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>6.8</td>
<td>No</td>
<td>Soft palate</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>7.0</td>
<td>Yes</td>
<td>Right lower eyelid</td>
<td>4500</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>9.4</td>
<td>Yes</td>
<td>Left neck</td>
<td>4500</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>9.4</td>
<td>Yes</td>
<td>Left orbit</td>
<td>5000</td>
</tr>
<tr>
<td>Chemo-therapy</td>
<td>WT</td>
<td>3.9</td>
<td>No</td>
<td>Right upper abdomen</td>
<td>1500</td>
</tr>
<tr>
<td></td>
<td>WT</td>
<td>4.8</td>
<td>No</td>
<td>Both lungs</td>
<td>1500</td>
</tr>
<tr>
<td></td>
<td>WT</td>
<td>5.0</td>
<td>No</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
</table>
4.4 TRISMUS

Limitation of mouth opening is seldom found, with only 4.5% of patients being classified with this problem (Table 4-8).

A Chi-squared analysis of the incidence of trismus in the three groups shows that there is a significant relationship (p < 0.001) with the head and neck irradiation group. Of the head and neck irradiation group, 17.2% present with trismus. Only 3.5% of the cranial irradiation group and none of the chemotherapy group have trismus, while 96.5% of the cranial irradiation group and all of the chemotherapy group have normal mouth opening.

As demonstrated in Table 4-9, all patients who have limitation of mouth opening had received cancer therapy at the age of 9 years or younger. Radiation doses range from 2400-cGy to 9100-cGy with a mean of 4167 cGy. Radiation fields involved specific areas such as the cranium, orbit, cheek, mandible, neck or, more generally, the whole body.
### Table 4-8  
**Trismus**

<table>
<thead>
<tr>
<th>Presence of Trismus</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>No</td>
<td>110</td>
<td>96.5</td>
<td>24</td>
<td>82.8</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>3.5</td>
<td>5</td>
<td>17.2</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100.0</td>
<td>29</td>
<td>100.0</td>
</tr>
</tbody>
</table>

$\chi^2 = 14.0, p = 0.0009$

### Table 4-9  
**Details of patients with trismus**

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
<th>Age at diagnosis (years)</th>
<th>Radiation field</th>
<th>Radiation dose (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial irradiation</td>
<td>ALL</td>
<td>1.8</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>ALL</td>
<td>3.2</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>ALL</td>
<td>6.2</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>8.0</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td>Head and neck irradiation</td>
<td>ALL</td>
<td>4.3</td>
<td>Cranium</td>
<td>2400</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>2.9</td>
<td>Total body</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>4.9</td>
<td>Left cheek</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>5.9</td>
<td>Mandible</td>
<td>6000</td>
</tr>
<tr>
<td></td>
<td>RMS</td>
<td>9.4</td>
<td>Left cheek</td>
<td>5000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left neck</td>
<td>4500</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Left orbit</td>
<td>5000</td>
</tr>
</tbody>
</table>
4.5 OCCLUSION

As shown in Table 4-10, 9.4% present with a normal occlusion, 77.1% of the study population present with a Class I malocclusion, 9.5% exhibit Class II malocclusion, and 3.5% have a Class III malocclusion. The occlusion of one patient in the head and neck irradiation group is undetermined because of disfigurement following mandibulectomy.

The distribution patterns of occlusion are similar in the three groups. Of the cranial irradiation group, 73.7% show Class I malocclusion, 13.2% exhibit normal occlusion, 10.5% Class II malocclusion and 2.6% Class III malocclusion. Of the chemotherapy group, 82.8% have Class I malocclusion, 6.9% have normal occlusion and 5.2% exhibit Class II and Class III malocclusion. Similarly, 79.3% of the head and neck radiation group show Class I malocclusion, 13.8% and 3.4% present with Class II and Class III malocclusion respectively.

Table 4-10 Occlusion

<table>
<thead>
<tr>
<th>Occlusion</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
<td>13.2</td>
<td>4</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td>9.4</td>
</tr>
<tr>
<td>Class I</td>
<td>84</td>
<td>73.7</td>
<td>48</td>
<td>82.8</td>
</tr>
<tr>
<td></td>
<td>155</td>
<td>77.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>12</td>
<td>10.5</td>
<td>4</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>9.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>3</td>
<td>2.6</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100.0</td>
<td>58</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>201</td>
<td>100.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4.6 ORTHODONTIC TREATMENT NEEDS

As shown in Table 4-11, 31.8% of this population need orthodontic treatment.

The need for orthodontic treatment in the three groups is similar to the total population. For the cranial irradiation group, 67.5% do not need treatment while 32.5% have orthodontic needs. For the chemotherapy group, 62.1% do not need treatment whilst 82.8% of the head and neck irradiation group do. Chi-squared analysis reveals no significant difference in need for orthodontic treatment between these three groups with $\chi^2 = 3.8$, $p = 0.14$.

<table>
<thead>
<tr>
<th>Orthodontic treatment needs</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>77</td>
<td>24</td>
<td>36</td>
<td>137</td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>5</td>
<td>22</td>
<td>64</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>29</td>
<td>58</td>
<td>201</td>
</tr>
</tbody>
</table>

$\chi^2 = 3.8$, $p = 0.14$
4.7 **DENTAL MATURITY**

For the assessment of dental age and/or dental maturity, 116 of 201 patients were reviewed. The mean chronological age of these patients is 12.7 years. The mean estimated dental age is 12.8 years. There is no significant difference between the dental and chronological age in this group of patients (**Table 4-12**). Patients were excluded from this assessment if they were older than 13 years at the time of diagnosis.

When examining the three groups, the analysis shows no significant difference between the dental and chronological age in either the head and neck irradiation or the chemotherapy groups. Interestingly, the dental age of the patients in the cranial irradiation group is significantly older than their chronological age, with $t = 4.9$; degrees of freedom=66; and $p < 0.0001$.

**Table 4-12** Dental and chronological ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Cranial irradiation (n=67)</th>
<th>Head and neck irradiation (n=13)</th>
<th>Chemotherapy (n=36)</th>
<th>Total (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X  SD</td>
<td>X  SD</td>
<td>X  SD</td>
<td>X  SD</td>
</tr>
<tr>
<td>Dental</td>
<td>13.5 2.0</td>
<td>11.2 4.7</td>
<td>12.3 3.4</td>
<td>12.8 3.0</td>
</tr>
<tr>
<td>Chronological</td>
<td>12.8 1.7</td>
<td>12.7 3.6</td>
<td>12.4 3.4</td>
<td>12.7 2.6</td>
</tr>
</tbody>
</table>

| Mean difference | 0.7 1.1                   | -1.5 5.6                          | -0.1 4.6            | 0.2 3.3       |
| t-value         | 4.9                       | -1.00                             | -0.2                | 0.6           |
| Degree of Freedom | 66 12                     | 35 115                            |                     |
| p-value         | < 0.0001                   | 0.36                              | 0.85                | 0.58          |

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4.8 DENTAL DEVELOPMENTAL ABNORMALITIES

As presented in Table 4-13, 65.6% of the study population develop a wide range of dental abnormalities. The severity ranges through mild (33.8%), moderate (19.9%), to severe (11.9%).

When considering the three groups separately, there was a difference in the distribution of percentage of patients within each group of the differing abnormalities (Table 4-13 and Figure 4-4). The percentage of patients with normal dentition is highest (36.2%) in the chemotherapy group, followed by the cranial irradiation group (24.6%). The head and neck irradiation group has the lowest percentage (6.9%) of patients with normal teeth. The occurrence of dental abnormalities for the cranial irradiation group (37.7%) and the chemotherapy group (29.3%) is similar, most patients being in the mild category. In contrast, most patients (62%) in the head and neck irradiation group exhibit moderate or severe dental defects. Chi-squared analysis demonstrates a significant difference in the severity of the developmental dental abnormalities between these three groups with \( \chi^2 = 29.5 \) and \( p = 0.0003 \).

4.8.1 Number of Abnormal Teeth per Person

When excluding the ineligible patients, the average number of abnormal teeth per person in the total study population is 9.3. The average number of abnormal teeth per affected patient in the three groups is different. The head and neck irradiation group presented with the highest average number (13.5 teeth per person), followed by the cranial irradiation group (9.5 teeth per person). The chemotherapy group possesses the lowest average number of abnormal teeth per person (6.5). As shown in Table 4-14, Kruskal-Wallis one-way analysis of variance demonstrates a significant difference in average number of abnormal teeth in these three groups with Kruskal-Wallis = 13.5 and \( p = 0.0012 \).
### Table 4-13  Dental developmental abnormalities

<table>
<thead>
<tr>
<th>Severity</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>24.6</td>
<td>2</td>
<td>6.9</td>
</tr>
<tr>
<td>Mild</td>
<td>43</td>
<td>37.7</td>
<td>8</td>
<td>27.6</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
<td>21.9</td>
<td>9</td>
<td>31.0</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>9.6</td>
<td>9</td>
<td>31.0</td>
</tr>
<tr>
<td>Undetermined</td>
<td>7</td>
<td>6.1</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>114</td>
<td>100.0</td>
<td>29</td>
<td>100.0</td>
</tr>
</tbody>
</table>

χ² = 29.5, p = 0.0003

### Table 4-14  Number of defective teeth in patients in different treatment groups

<table>
<thead>
<tr>
<th></th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of defective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>teeth</td>
<td>1014</td>
<td>378</td>
<td>314</td>
<td>1706</td>
</tr>
<tr>
<td>Number of patients</td>
<td>107</td>
<td>28</td>
<td>48</td>
<td>183</td>
</tr>
</tbody>
</table>

Kruskal-Wallis = 13.5, p = 0.0012
Results

Figure 4-4  Percentage of patients in different treatment groups by Severity of dental abnormalities

Figure 4-5  Percentage of patients in different treatment groups by Type of dental abnormalities
4.8.2 Types of Dental Abnormalities

Table 4-15 and Figure 4-5 illustrate the percentage of patients manifesting different types of dental abnormalities in both the total study population and the three groups. Shortening of the roots is the most common defect found affecting 62.8% of the total group. As far as the three study groups are concerned, 66.4% of the cranial irradiation group, 82.1% of the head and neck irradiation group, and 43.8% of the chemotherapy group show root shortening.

In the total population the second most frequent abnormality is tapering of the root (39.9%), followed by microdontia (30.6%), absent tooth (18.0%), absent root (4.9%) and taurodontia (1.1%).

For the cranial irradiation group, the second most frequent defect is root tapering (43.0%), followed by microdontia (30.8%), absent tooth (15.0%), and taurodontia (0.9%). There were no patients in this group who had root agenesis.

Root tapering is also the second most frequent abnormality, involving 53.6% of patients, in the head and neck irradiation group. It is followed by microdontia (39.3%). Tooth and root agenesis equally affect 32.1% of patients in this group. It is noted that all patients presenting complete root absence are in this group (32.1%).

As far as the chemotherapy group is concerned, the second most common defect is microdontia and root tapering which affects 25.0% of patients. Absent teeth and taurodontia involve 16.7% and 2.1% of the patients respectively.
### Results

**Table 4-15** Number and percentage of patients in different types of dental developmental abnormalities

<table>
<thead>
<tr>
<th>Type of defect</th>
<th>Cranial irradiation (107)</th>
<th>Head and neck irradiation (28)</th>
<th>Chemotherapy (48)</th>
<th>Total (183)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Tooth agenesis</td>
<td>16</td>
<td>15.0</td>
<td>9</td>
<td>32.1</td>
</tr>
<tr>
<td>Microdontia</td>
<td>33</td>
<td>30.8</td>
<td>11</td>
<td>39.3</td>
</tr>
<tr>
<td>Shortened root</td>
<td>71</td>
<td>66.4</td>
<td>23</td>
<td>82.1</td>
</tr>
<tr>
<td>Tapered root</td>
<td>46</td>
<td>43.0</td>
<td>15</td>
<td>53.6</td>
</tr>
<tr>
<td>Taurodontia</td>
<td>1</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Absent root</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>32.1</td>
</tr>
</tbody>
</table>

**Figure 4-6** Percentage of defective teeth by Tooth type- Total study population
Results

Figure 4-7  Percentage of defective teeth by Tooth type- Cranial irradiation group

![Graph showing percentage of defective teeth by tooth type for cranial irradiation group.]

<table>
<thead>
<tr>
<th>Tooth type</th>
<th>Rt-7</th>
<th>Rt-6</th>
<th>Rt-5</th>
<th>Rt-4</th>
<th>Rt-3</th>
<th>Rt-2</th>
<th>Rt-1</th>
<th>Lt-1</th>
<th>Lt-2</th>
<th>Lt-3</th>
<th>Lt-4</th>
<th>Lt-5</th>
<th>Lt-6</th>
<th>Lt-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary</td>
<td>97.5</td>
<td>75.9</td>
<td>62</td>
<td>51.9</td>
<td>41.8</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
<td>31.6</td>
</tr>
<tr>
<td>Mandibular</td>
<td>69.6</td>
<td>29.1</td>
<td>148.1</td>
<td>45.6</td>
<td>25.3</td>
<td>15.2</td>
<td>13.9</td>
<td>13.9</td>
<td>15.2</td>
<td>26.6</td>
<td>45.6</td>
<td>46.8</td>
<td>31.6</td>
<td>69.6</td>
</tr>
</tbody>
</table>

Figure 4-8  Percentage of defective teeth by Tooth type- Head & neck irradiation group

![Graph showing percentage of defective teeth by tooth type for head & neck irradiation group.]

<table>
<thead>
<tr>
<th>Tooth type</th>
<th>Rt-7</th>
<th>Rt-6</th>
<th>Rt-5</th>
<th>Rt-4</th>
<th>Rt-3</th>
<th>Rt-2</th>
<th>Rt-1</th>
<th>Lt-1</th>
<th>Lt-2</th>
<th>Lt-3</th>
<th>Lt-4</th>
<th>Lt-5</th>
<th>Lt-6</th>
<th>Lt-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary</td>
<td>61.5</td>
<td>53.8</td>
<td>65.4</td>
<td>53.8</td>
<td>61.5</td>
<td>33.5</td>
<td>10.1</td>
<td>10.1</td>
<td>38.5</td>
<td>61.5</td>
<td>57.7</td>
<td>65.4</td>
<td>65.6</td>
<td>61.5</td>
</tr>
<tr>
<td>Mandibular</td>
<td>57.7</td>
<td>53.8</td>
<td>69.2</td>
<td>69.2</td>
<td>50</td>
<td>23.1</td>
<td>23.1</td>
<td>23.1</td>
<td>26.9</td>
<td>57.7</td>
<td>76.8</td>
<td>73.1</td>
<td>57.7</td>
<td>65.4</td>
</tr>
</tbody>
</table>

138
Figure 4-9  Percentage of defective teeth by Tooth type- Chemotherapy group

Figure 4-10  Number of patients with different severity of dental abnormalities by Age at diagnosis
4.8.3 Distribution Pattern of Dental Abnormalities

A distribution pattern for dental abnormalities in different tooth types is investigated. **Figure 4-6** demonstrates the distribution pattern of dental abnormalities for different tooth types. The maxillary teeth in general, and the maxillary posterior teeth in particular, are more affected than the corresponding mandibular teeth. The most frequently damaged tooth type is the maxillary second molar, followed by the maxillary first molar, the maxillary premolar, the mandibular premolar, the maxillary canine, the mandibular first molar, the maxillary incisor, and the mandibular canine. The least commonly affected tooth type are the mandibular incisors. Among the posterior teeth, the mandibular first molars are the least affected tooth type. When inspecting the three groups, the cranial irradiation group manifests the same distribution pattern (**Figure 4-7**).

**Figure 4-8** presents a different distribution pattern of dental abnormalities in different tooth types in the head and neck irradiation group. The mandibular and posterior teeth are affected more than the maxillary and anterior ones. The most frequently altered tooth type is the mandibular premolar, followed by the maxillary premolar, the second molars, the canine, the first molars, and the mandibular incisors. The least commonly affected tooth type is the maxillary incisors.

As shown in **Figure 4-9**, distribution pattern of dental defects in different tooth types in the chemotherapy group differs from the previous groups. The most frequently affected tooth type is the first premolar, followed by the first molars, the maxillary lateral incisor, the second premolars, the second molars, and the canines. The least commonly altered tooth type is the mandibular incisor.

In total study group, the maxillary teeth are significantly affected more often than the mandibular ones and the posterior teeth are significantly altered more frequently than the anterior ones, as demonstrated in **Table 4-16**. Only the cranial irradiation group displays the same significant findings. In the head and neck and chemotherapy groups, there is no significant difference between the percentage of abnormal teeth found in the maxilla.
and the mandible. However, as with the result of the cranial radiation group, the posterior teeth are significantly altered more frequently than the anterior ones.

Independent variables that could have had influence, including sex, age at diagnosis, radiation site, radiation dose, chemotherapeutic protocol, and treatment duration, were analysed by logistic regression technique. The results show that the most important variables, associated with the occurrence of dental abnormalities, are the age at diagnosis, radiation site, radiation dose, and chemotherapeutic protocol.

4.8.4 Dental Abnormalities and Age at Diagnosis

Figure 4-10 shows the number of patients with differing severity of dental abnormalities at different ages at diagnosis. In the normal and mild severity groups, the largest concentration of patients is children diagnosed between 3 and 5 years of age. For the more severely affected children (moderate and severe groups), the age of diagnosis is between 1 and 3 years of age. Since the number of patients in every category decreases between the age of 5 and 6 years of age, the patients (excluding the undetermined group) were grouped into two different categories, viz., age at diagnosis; less than 6 years and greater than 6 years of age. As shown in Table 4-17, Chi-squared analysis demonstrates a highly significant difference in the total study population with $\chi^2 = 22.4$ and $p < 0.0001$. Patients who started the treatment at younger than 6 years old, present more severe dental abnormalities than those who commenced their treatment at an older age. Only 20% of the patients, younger than 6 years old at diagnosis, have normal teeth while almost half (43.5%) of the 6 year and older children show normal teeth (Figure 4-11).

Figures 4-12, 4-13 and 4-14, illustrate that there is a similarity in each subgroup. The percentage of patients with normal dentition in the older group is more than that in the younger groups. Interestingly, the findings are not consistent when separating the study population into three subgroups. Significant differences exist only in the cranial and head and neck irradiation groups but not in the chemotherapy group, as shown in Table 4-17.
Table 4-16  Percentage of abnormal teeth in different tooth types

<table>
<thead>
<tr>
<th>Group</th>
<th>Tooth type</th>
<th>Normal teeth</th>
<th>Abnormal teeth (%)</th>
<th>Total teeth</th>
<th>$\chi^2$, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maxillary</td>
<td>766</td>
<td>977 (56.0)</td>
<td>1743</td>
<td></td>
</tr>
<tr>
<td>Mantibular</td>
<td>1024</td>
<td>729 (41.5)</td>
<td>1753</td>
<td></td>
<td>72.6, &lt; 0.0001</td>
</tr>
<tr>
<td>Total</td>
<td>Anterior</td>
<td>1056</td>
<td>487 (31.6)</td>
<td>1543</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>734</td>
<td>1219 (62.4)</td>
<td>1953</td>
<td>327.2, &lt; 0.0001</td>
</tr>
<tr>
<td>Cranial irradiation</td>
<td>Maxillary</td>
<td>439</td>
<td>622 (58.6)</td>
<td>1061</td>
<td>103.5, &lt; 0.0001</td>
</tr>
<tr>
<td>Mandibular</td>
<td>681</td>
<td>392 (36.5)</td>
<td>1073</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck irradiation</td>
<td>Anterior</td>
<td>681</td>
<td>253 (27.1)</td>
<td>934</td>
<td>276.5, &lt; 0.0001</td>
</tr>
<tr>
<td>Posterior</td>
<td>439</td>
<td>761 (63.4)</td>
<td>1200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo-therapy</td>
<td>Maxillary</td>
<td>146</td>
<td>189 (56.4)</td>
<td>335</td>
<td>0.01, 0.93</td>
</tr>
<tr>
<td>Mandibular</td>
<td>148</td>
<td>189 (56.1)</td>
<td>337</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior</td>
<td>178</td>
<td>121 (40.5)</td>
<td>299</td>
<td>53.4, &lt; 0.0001</td>
</tr>
<tr>
<td>Posterior</td>
<td>116</td>
<td>257 (68.9)</td>
<td>373</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maxillary</td>
<td>181</td>
<td>166 (47.8)</td>
<td>347</td>
<td>1.4, 0.25</td>
</tr>
<tr>
<td></td>
<td>Manibular</td>
<td>195</td>
<td>148 (43.1)</td>
<td>343</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior</td>
<td>197</td>
<td>113 (36.4)</td>
<td>310</td>
<td>17.9, 0.000023</td>
</tr>
<tr>
<td></td>
<td>Posterior</td>
<td>179</td>
<td>201 (52.9)</td>
<td>380</td>
<td></td>
</tr>
</tbody>
</table>
Table 4-17  Dental abnormalities in patients receiving cancer treatment before and after the age of 6 years

<table>
<thead>
<tr>
<th>Severity of dental abnormalities</th>
<th>Cranial irradiation n/%</th>
<th>Head and neck irradiation n/%</th>
<th>Chemotherapy n/%</th>
<th>Total n/%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6  ≥ 6</td>
<td>&lt;6  ≥ 6</td>
<td>&lt;6  ≥ 6</td>
<td>&lt;6  ≥ 6</td>
</tr>
<tr>
<td>Normal</td>
<td>14/19.2 14/41.2</td>
<td>0/0  2/20.0</td>
<td>10/34.3 11/61.1</td>
<td>24/19.8 27/43.5</td>
</tr>
<tr>
<td>Mild</td>
<td>27/37.0 16/47.1</td>
<td>3/16.7 5/50.0</td>
<td>11/36.7 6/33.3</td>
<td>41/33.9 27/43.5</td>
</tr>
<tr>
<td>Moderate &amp; severe</td>
<td>32/43.8 4/11.8</td>
<td>15/83.3 3/30.0</td>
<td>9/30.0 1/5.6</td>
<td>56/46.3 8/12.9</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>12.0</td>
<td>8.9</td>
<td>5.2</td>
<td>22.4</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0025</td>
<td>0.011</td>
<td>0.073</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Figure 4-11  Distribution of severity of dental abnormalities in the total population, receiving cancer treatment before and after the age of 6 years
Figure 4-12 Distribution of severity of dental abnormalities in the cranial irradiation group, receiving cancer treatment before and after the age of 6 years

![Graph showing severity of dental abnormalities]

<table>
<thead>
<tr>
<th>Severity of dental abnormality</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate &amp; Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>19.2</td>
<td>37</td>
<td>43.8</td>
</tr>
<tr>
<td>&gt;= 6</td>
<td>41.2</td>
<td>47.1</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Figure 4-13 Distribution of severity of dental abnormalities in the head & neck irradiation group, receiving cancer treatment before and after the age of 6 years

![Graph showing severity of dental abnormalities]

<table>
<thead>
<tr>
<th>Severity of dental abnormality</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate &amp; Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>0</td>
<td>16.7</td>
<td>83.3</td>
</tr>
<tr>
<td>&gt;= 6</td>
<td>20</td>
<td>50</td>
<td>30</td>
</tr>
</tbody>
</table>
4.8.5 Dental Abnormalities and Radiation Dose

Since there is a wide variation in radiation dose, only 100 patients in the cranial irradiation group were included in this investigation. Table 4-18 and Figure 4-15 show the association between severity of dental abnormalities and radiation dose. Thirty-six children in this group received 1800-cGy cranial irradiation while 64 patients had 2400-cGy irradiation. Patients, receiving 2400-cGy cranial irradiation, demonstrate severe dental abnormalities significantly more often than the patients, receiving 1800-cGy cranial irradiation, with $\chi^2 = 15.6$ and $p = 0.0004$. Approximately 40% (n=27) of the patients, receiving 2400-cGy cranial irradiation, exhibit either moderate or severe dental defects while only 13.9% (n=5) of those receiving 1800-cGy cranial irradiation exhibited similar defects. In other words, only 14.1% of the patients, receiving 2400-cGy cranial irradiation, show normal teeth whereas 47.2% of those receiving 1800-cGy cranial irradiation do.
Table 4-18  Dental developmental abnormalities and radiation dose

<table>
<thead>
<tr>
<th>Severity</th>
<th>1800-cGy irradiation</th>
<th>2400-cGy irradiation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Normal</td>
<td>17</td>
<td>47.2</td>
<td>9</td>
</tr>
<tr>
<td>Mild</td>
<td>14</td>
<td>38.9</td>
<td>28</td>
</tr>
<tr>
<td>Moderate &amp; severe</td>
<td>5</td>
<td>13.9</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100.0</td>
<td>64</td>
</tr>
</tbody>
</table>

Figure 4-15  Distribution of dental abnormalities in the cranial irradiation group, receiving different radiation doses.
4.8.6 Dental Abnormalities and Chemotherapeutic Protocol

Eighty-five patients in the cranial irradiation group were included in this analysis. Fifty-nine of them were treated with LSA$_2$L$_2$ chemotherapeutic protocol and 26 of them were treated by BFM protocol. Table 4-19 and Figure 4-16 present the association between the severity of dental abnormalities and these two chemotherapeutic protocols. Chi-squared analysis reveals a significant difference in the severity of dental defects between patients receiving LSA$_2$L$_2$ and BFM protocols, with $\chi^2 = 10.4$ and $p = 0.005$. Almost half of the patients who were treated by LSA$_2$L$_2$ protocol develop either moderate or severe dental abnormalities while only 19.2% of those treated with the BFM protocol do. Likewise, only 13.6% of patients in LSA$_2$L$_2$ group have normal teeth whereas 42.3% of patients in BFM group do.
Results

Table 4-19  Dental developmental abnormalities and chemotherapeutic protocol

<table>
<thead>
<tr>
<th>Severity</th>
<th>LSA_2L_2</th>
<th>BFM</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Normal</td>
<td>8</td>
<td>13.6</td>
<td>11</td>
</tr>
<tr>
<td>Mild</td>
<td>23</td>
<td>39.0</td>
<td>10</td>
</tr>
<tr>
<td>Moderate &amp; severe</td>
<td>28</td>
<td>47.4</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>100.0</td>
<td>26</td>
</tr>
</tbody>
</table>

χ² =10.4,  p = 0.005

Figure 4-16  Distribution of dental abnormalities in the cranial irradiation group, receiving different chemotherapeutic protocols.

---

**Percentage of patients**

<table>
<thead>
<tr>
<th>Severity of dental abnormality</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate &amp; severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSA_2L_2</td>
<td>13.6</td>
<td>39</td>
<td>47.5</td>
</tr>
<tr>
<td>BFM</td>
<td>42.3</td>
<td>38.5</td>
<td>19.2</td>
</tr>
</tbody>
</table>
4.9 MEDICAL COMPLICATIONS

As presented in Table 4-20, medical complications have been frequently found in this study population. There are 162 patients (80.6%) in the study population presenting some medical complications. Only 33 patients (16.4%) are free of any medical complications, whilst for six patients (3.0%) no recent information was available. The presence of medical complications (96.6%) in the head and neck irradiation group occurs more frequently than in the cranial irradiation (78.9%) or the chemotherapy group (75.9%). Chi-squared analysis, however, shows no significant difference between these three groups with $\chi^2 = 29.5$ and $p = 0.058$.

As demonstrated in Table 4-21 and Figure 4-17, growth hormone deficiency, learning difficulty, hypogonadism, and musculoskeletal disorders are common late effects, involving approximately one third of the study population. Growth hormone deficiency, learning difficulty, and hypogonadism are frequent disorders in both the cranial and the head and neck irradiation groups but less common in the chemotherapy group. On the other hand, musculoskeletal disorders, such as asymmetrical skeletal structures, tissue or organ atrophy, scoliosis, and osteoporosis, are found more commonly in the head and neck irradiation and chemotherapy groups than the cranial irradiation group.

Another important late effect, hypothyroidism, affects 13.3% of the patients and is found more frequently in the head and neck irradiation group. Alopecia, an aesthetic and social problem, affects 12.3% of total patients and is predominantly found in the cranial irradiation group. Neural complications, such as hearing loss, involve 6.2% of the patients, particularly from those in the head and neck irradiation group. Complications of the gastrointestinal tract, such as radiation colitis, and pulmonary problems also exist in approximately 2% of the total patients, but are not found in the head and neck irradiation group. Other problems include chromosomal damage (one patient, cranial irradiation group), a cataract (one patient, head and neck irradiation group), and a secondary malignancy (one patient, chemotherapy group).
Table 4-20  Medical complications

<table>
<thead>
<tr>
<th>Medical complications</th>
<th>Cranial irradiation</th>
<th>Head and neck irradiation</th>
<th>Chemotherapy</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>19.3</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>Yes</td>
<td>90</td>
<td>78.9</td>
<td>28</td>
<td>96.6</td>
</tr>
<tr>
<td>Total</td>
<td>114</td>
<td>100.0</td>
<td>29</td>
<td>100.0</td>
</tr>
</tbody>
</table>

χ² = 29.5, p = 0.058

Figure 4-17  Percentage of patients in different treatment groups by Type of medical complications
### Table 4-21  Types of medical complications

<table>
<thead>
<tr>
<th>Medical complications</th>
<th>Cranial irradiation (112)</th>
<th>Head and neck irradiation (29)</th>
<th>Chemotherapy (54)</th>
<th>Total (195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone deficiency</td>
<td>49  43.8</td>
<td>10  34.5</td>
<td>1  1.8</td>
<td>60  30.8</td>
</tr>
<tr>
<td>Learning difficulty</td>
<td>47  42.0</td>
<td>10  34.5</td>
<td>7  13.0</td>
<td>64  32.8</td>
</tr>
<tr>
<td>Gonad function</td>
<td>37  33.0</td>
<td>13  44.8</td>
<td>13  24.1</td>
<td>63  32.3</td>
</tr>
<tr>
<td>Thyroid function</td>
<td>14  12.5</td>
<td>10  34.5</td>
<td>2  3.7</td>
<td>26  13.3</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>12  10.7</td>
<td>17  58.6</td>
<td>23  42.6</td>
<td>52  26.7</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23  20.5</td>
<td>1  3.4</td>
<td>0  0</td>
<td>24  12.3</td>
</tr>
<tr>
<td>Nervous system</td>
<td>3   2.7</td>
<td>8   27.6</td>
<td>2  3.7</td>
<td>12  6.2</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>3   2.7</td>
<td>0   0</td>
<td>2  3.7</td>
<td>5  2.6</td>
</tr>
<tr>
<td>Pulmonary system</td>
<td>3   2.7</td>
<td>0   0</td>
<td>1  1.8</td>
<td>4  2.1</td>
</tr>
<tr>
<td>Others</td>
<td>1   0.9</td>
<td>1   3.4</td>
<td>1  1.8</td>
<td>3  1.5</td>
</tr>
</tbody>
</table>
4.9.1 Medical Complications and Dental Abnormalities

Excluding those patients with unknown medical complications and undetermined dental abnormalities, 178 patients enable a possibility of assessing an association between the presence of medical late effects and the severity of dental disturbances. Table 4-22 demonstrates a significant association between these variables, with $\chi^2 = 9.5$ and $p = 0.0088$. Almost 40.0% of patients with both moderate and severe dental defects present some medical complications.

Table 4-22 Medical complications and severity of dental abnormalities

<table>
<thead>
<tr>
<th>Severity</th>
<th>Medical Complications</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absent n %</td>
<td>Present n %</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>13 52.0</td>
<td>35 22.8</td>
<td>48 27.0</td>
</tr>
<tr>
<td>Mild</td>
<td>7 28.0</td>
<td>59 38.6</td>
<td>66 37.0</td>
</tr>
<tr>
<td>Moderate &amp; severe</td>
<td>5 20.0</td>
<td>59 38.6</td>
<td>64 36.0</td>
</tr>
<tr>
<td>Total</td>
<td>25 100.0</td>
<td>66 100.0</td>
<td>178 100.0</td>
</tr>
</tbody>
</table>

$\chi^2 = 9.5$, $p = 0.0088$
CHAPTER FIVE

DISCUSSION

5.1 SAMPLE

The sample size of this study is relatively large when compared with many previous studies. Although acute lymphoblastic leukaemia (ALL) comprises more than half of the study population, cancer diagnosis was not a criteria in grouping patients for analysis. Since the localised effects of radiotherapy are well recognised, the absence or presence of irradiation to the head and neck region and the site of irradiation were used to group the population in this study. This differs from previous studies as many of them focused on ALL and assumed that only chemotherapy was associated with causing dental abnormalities (Welbury et al 1984, Maguire et al 1987, Purdell-Lewis et al, 1988). Some authors described chronic dental complications only for patients receiving chemoradiotherapy for soft tissue sarcomas of head and neck (Fromm et al 1986, Berkowitz et al 1989).

Generally in observational studies like this, it is almost impossible to obtain matched samples for accurate comparison. Variations in disease diagnosis, stage of disease, treatment protocols, and individual patient's response are all constraints of these studies and lead to difficulties in grouping patients and obtaining conclusive results. Therefore many studies only describe the findings in individual patients, although they had specified a group of patients (Fromm et al 1986, Dahllof et al 1988). Other reports have concentrated on a particular cancer, such as ALL (Rosenberg et al 1987, Sonis et al 1990). One should also be aware that the treatment protocols for the same disease also vary as well as the individual response to the treatment and thus results have to be interpreted with this in mind. For example, some children do not complete the full schedule of a given treatment protocol. This is because they can become too sick to continue their treatment and will pick up their regimen again at a later stage in the cycle.
The sample size and the classifying criteria used in this study provide a more precise investigation of the oral complications in patients who are treated with differing types of anticancer therapy. As well comparison with previous studies is improved. For example, results obtained from the cranial irradiation group can be compared with the results from other studies which have focussed on children with ALL. The number of patients in the chemotherapy group is large enough to draw some conclusions about the effects on the orofacial structures of chemotherapy alone. The small number of patients in the head and neck irradiation group allowed only descriptive comments to be made.

5.2 ORAL HEALTH

5.2.1 Dental Caries
In the present study, approximately half of the study population have a low caries level (0-3 dmft, DMFT). There is no statistically significant difference in caries incidence among the cranial irradiation, the head and neck irradiation and the chemotherapy groups, although more than half (69%) of the head and neck irradiation group present higher caries level (>3 dmft, DMFT). This is probably due to the small sample size.

It would have been ideal to include a control group, matched for age, sex, and social class, but this was not feasible. It is difficult to compare the result of caries status from this study to other studies (Maguire et al 1987, Purdell-Lewis et al 1988) which used dmf or DMF indices instead of caries level for caries diagnosis, but comparison may be made using the percentage of the patients with sound dentition. The caries status of this study group seems to be similar to that of the normal population since the percentage of the patients with sound dentition in this study population is 29.4%, compared with 28% of 12-year-old Australian children, predicted by Spencer and Lewis (1987). This is in line with many studies which found no significant difference in the caries prevalence for the patients surviving childhood cancer, compared either with the "national average" (Welbury et al 1984, Fleming and Kinirons 1986, Nunn et al, 1991) or with a control group (Maguire et al 1987, Pajari et al 1988a, Näsman et al 1994).
The present results are, however, in disagreement with the result of Bertolone et al (1981). They found a slightly higher caries experience than the national average for leukaemia patients in remission. As well, Purdell-Lewis et al (1988) also reported a threefold difference in the prevalence of initial carious lesions in their study children, compared with the general population.

Overall studies of caries prevalence in survivors of childhood cancer have been inconclusive. For example, this present study population may, in fact, have a higher caries prevalence than detected, due to the method used for caries assessment. A more detailed analysis using DMF(S) may reveal a different result. The factors behind a possible high caries activity in children surviving childhood cancer may lie in the disease itself and/or in the cancer therapy. The long-term used of sugar-based paediatric medicines may increase caries experience (Roberts and Roberts 1979, Feigal 1984). Some anti-cancer agents cause transient xerostomia and vomiting (Ostchega 1980, Lavelle et al 1984), and thus reduce the oral pH. During cancer treatment, most of the patients also have vomiting episodes. Bad taste, oral ulcers and the families' concerns may favour sweet, cariogenic food. Serious diseases may also lead to poorer levels of oral hygiene. It is also well known that the caries incidence is very high after tumouricidal irradiation to the jaws and/or salivary glands (Brown et al 1975, Dreizen et al 1977, NaKamoto 1979). All, or one, of these reasons could lead to higher dmf and DMF surface scores among cancer patients, especially during the active treatment.

The inconclusive nature of the prevalence of dental caries in the survivors of childhood cancer is contrasted with the situation for adults being treated for cancer. Severe radiation caries is frequently found in adults who receive radiotherapy. However, childhood cancers differ from adult ones in many aspects. Importantly many children can be cured with chemotherapy. Also, radiotherapy, when included in the treatment regime, mostly does not directly involve the jaws and/or salivary glands, however the role of radiation scatter from cranial irradiation cannot be overlooked. Also the dosage used for children is usually lower. Child patients commonly receive treatment when they are in
the primary dentition stage (an average age of 5 years in this study). They are usually assessed dentally at least 5 years later, in the permanent dentition stage (approximately 15 years of age in this study). It is therefore likely that they will have a caries prevalence similar to those of the normal population. Another important factor is oral health education for the parents since the parents of children suffering cancer are usually very motivated and well informed about their children's health and are willing to follow all advice that will help their children to have better quality of life. This may decrease caries to a level better than the community average.

To accurately ascertain the exact caries problem for these patients will require further research. A better caries assessment method, a matched control group, and a larger sample size should be employed. From a practical dental point of view, a preventive program for good oral health should always be emphasised for all such patients not only for reasons of preventing dental caries but also for reasons of maintaining periodontal health. The maintenance of periodontal health is especially relevant for these patients who often have a variety of root malformation.

5.2.2 Periodontal status
The result from this study suggests that most of these patients (>60%) present with gingivitis. Periodontitis is rarely found. There is no statistically significant difference in periodontal status among the cranial irradiation, the head and neck irradiation and the chemotherapy groups.

It is difficult to employ this finding to confidently compare the periodontal status of this study group with that of the normal population. This is because we did not have a matched control group to compare with. Also comparison with the national figures is inappropriate as different appraisal methods have been used. However a general overview reveals that the percentage of patients with normal periodontium (29.4%) is less than that reported (43.6%) for 15-19 year old persons in the national oral health survey (Barnard 1993 p107). The percentage of patients with gingivitis (66.6%) is also
greater. The reported level of periodontitis is generally consistent with the national data (4.0% compared with 4.6%).

The implication of a greater prevalence of periodontal disease in this study disagrees with previous studies (Welbury et al 1984, Fleming and Kinirons 1986) which reported no difference in soft tissue and gingival condition between patients with previous cancer therapy and the general population. Their assessment was, however, based on the gingival index of Loe (1967) which is more precise than the evaluation method used in this study. Thus, there could have been an under- or over-estimation in this study. Despite the method of periodontal assessment used, it appears that a greater number of children have early signs of periodontal disease.

Although there is no supporting long-term study, the results imply a possibility that these patients develop more periodontal diseases, especially if their oral hygiene practices are neglected. A routine preventive program is very important and should be started as early as possible. Such a program should be tailored individually for each patient. Dentists should also be aware that these patients frequently have learning difficulties and require more time and effort to develop understanding and competency of the necessary skills.

Future research should target the mechanisms of cancer treatment injury to periodontium at the molecular and cellular level and determine the presence of periodontal disease in these patients who have various types of root malformation.
5.3 FACIAL DEFORMITY

In this study, a low incidence of facial deformity is found in all groups of patients. The patients treated with chemotherapy and radiotherapy to the face and neck regions (the head and neck irradiation group) show obvious facial deformity, significantly more often (approximately half of this group) than patients either receiving chemotherapy plus cranial irradiation or those having chemotherapy alone without irradiation to any part of the head and neck. Such facial deformity for the head and neck irradiation group may be due to the fact that all patients in this group had surgery performed.

The subjective method of facial evaluation used in this study is similar to some previous studies (Guyuron et al 1983, Jaffe et al 1984, Fromm et al 1986) which also found half, or more than half, of the patients receiving radiotherapy to the head and neck presented facial deformities. Also this result is similar to that reported by Fromm et al (1986) in which facial deformity occurs more frequently in patients, being 9 years or younger at diagnosis. Contrastingly in this study, not all of the patients, 9 years or younger at diagnosis, demonstrate facial deformity. This difference compared to other studies may be due to differences in the criteria used to evaluate the study population.

When considering the cranial irradiation group, the result concerning facial deformity differs from that of Dahllöf et al (1989b) who found significantly retarded growth in the craniofacial skeleton in children conditioned with TBI, but not in those not conditioned with TBI. In this present study, some patients who had not received TBI have distorted facial morphology. Although looking at a similar population, the findings of the present study can not be correlated to that of Sonis et al (1990), again due to the different criteria used. Sonis et al (1990) reported a significantly deficient mandibular development in 18 of 20 of patients who received chemotherapy plus 2400-cGy cranial irradiation before the age of 5 years. They, however, did not mention any change in facial morphology such that facial aesthetics were affected. In this present study, facial deformity was found in patients, both younger and older than 5 years old, at diagnosis, and in those children
receiving either 1800- or 2400-cGy cranial irradiation.

Unexpectedly, facial distortion is also exhibited by several patients who did not have radiotherapy to any part of head and neck. This is possibly explained by genetic variation, individual patient's response to chemotherapy, or the effect of scattered radiation.

From these results, one can suggest that facial deformity is not an uncommon problem in the survivors of childhood cancer. It does not occur only in patients, having chemoradiotherapy of head and neck but also in those, receiving chemotherapy alone. Management of such facial deformity requires the collaboration of several specialists, including the oncolgist, plastic surgeon, maxillofacial surgeon and an orthodontist. Furthermore, endodontic, prosthodontic, and periodontic assessments may be needed so that the best functional and aesthetic results can be accomplished.

5.4 TRISMUS

In this study, limitation of mouth opening is, although not common, another consequence occurring in survivors of childhood cancer. It is, however, not found in patients, receiving chemotherapy alone. Most (5 of 9) affected patients were diagnosed with rhabdomyosarcoma. Other diagnoses included acute lymphoblastic leukaemia and non-Hodgkin's lymphoma. All affected patients have received chemotherapy and high-dose radiation to the head and neck before the age of 9 years.

Although there are many case reports about the consequences of cancer treatment in childhood, only a few of them have mentioned trismus. The findings, from this study concerning the head and neck irradiation group, agree with that from a case report by Carl and Wood (1980). The patient in their report developed trismus after having surgery, chemotherapy and high dosage radiation to an area close to the temporomandibular joint at the age of 9 years.
Discussion

The findings in this study are different from those reported by Welbury et al (1984) and Maguire et al (1987). Welbury et al (1984) did not find any abnormality of mouth opening in 64 patients in long term remission from childhood malignancy while this study finds trismus in 4.5% of the study population. Measuring maximal interincisal distance, Maguire et al (1987) detected no difference in mouth opening between the long-term survivors of childhood leukaemia and their siblings. However, in this study, trismus was defined as being present with an interincisal distance of less than 40 mm. This may explain the differences compared to Maguire et al in that their group may have had cases of interincisal opening of less than 40 mm, but if they matched their siblings they were not scored as having trismus.

From a dental clinical point of view, trismus is an important sequelae which should be considered in the management of survivors of childhood cancer, especially those having irradiation to the head and neck. Trismus complicates proper oral hygiene practice and all dental procedures. Interestingly, it should be noted that these nine patients do not generally have good oral health. None is caries free, with four of them having caries at level 3, two at level 2, and 3 at level 1. Periodontal status is also poor, with seven having gingivitis and two having periodontitis.

5.5 OCCLUSION

Although statistical analysis was not carried out, our clinical impression was that there was no difference in malocclusion between the cranial irradiation, head and neck and chemotherapy groups. The percentage of malocclusion is, however, high in all three groups.

This result differs from Welbury et al (1984). They found no variation in occlusion from the normal average in 64 patients, having chemotherapy and radiation only to the cranium, not to the head and neck. As well, Jaffe et al (1984) reported abnormal occlusal relationships in only some of the patients treated with chemotherapy and radiation to the
head and neck, not in the leukaemic patients. In contrast, Maguire and others (1987) noted significantly more abnormal occlusion in patients with solid tumours, compared with the patients with leukaemia. None of these studies, however, described their criteria for classifying malocclusion. These variations in reported results, therefore, are most likely due to the different criteria used.

When considering the need for orthodontic treatment, the percentage of patients who need treatment (31.8%) is not as high as the percentage of patients with malocclusion (approximately 90%). It is, however, higher than the 26.1% of 15 to 19-year-old persons in the normal population who need treatment (Barnard 1993 p 111).

The high prevalence of malocclusion in these patients suggests that they may also be more susceptible to dental diseases if proper oral hygiene practices are ignored. The variety of malformed roots and crowns is important and must be taken into consideration when planning orthodontic management. For example, the amount and direction of applied force, the need for space analysis, and growth prediction are just some of the areas involved.

5.6 DENTAL MATURITY

The results indicate that chemotherapy and radiation to the head and neck, given to children with malignancies does not affect the dental development in terms of dental maturity. Dental maturity in the cranial irradiation group is statistically significantly different (p<0.001) from their chronological age, although this is not clinically manifest to any degree.

Not many follow-up studies have been carried out on the effects of cancer therapy on dental maturity. Two previous studies by Pajari et al (1988b) and Dahllöf et al (1989a) have examined similar study populations. They investigated patients who were given chemotherapy with and without cranial irradiation and used the same method for
assessing dental maturity. They found no significant difference between the dental and chronological age in children receiving cancer therapy compared with healthy controls. In contrast to those two studies, the findings of the present study show that the dental age of the patients in the cranial irradiation group is significantly older than their chronological age. This difference (approximately 8 months), however, does not cause any lasting clinical problem.

It should be noted that mean dental age of the patients from this study and two previous studies are older than mean chronological age either of themselves (Dahllöf et al 1989a) or of the healthy controls (Pajari et al 1988b). This concurrence of results can probably be explained by the overestimation of the dental age using the scoring system of Demirjian and Goldstein (1976). This was discussed by Hägg and Matsson (1985) and Staaf et al (1991). If that explanation is correct, one should be aware that the dental age in the head and neck irradiation and the chemotherapy groups may become clinically more delayed than their chronological age.

**Figure 5-1** displays an example of delayed dental maturity in one patient from the chemotherapy group. This female patient received chemoradiotherapy for rhabdomyosarcoma at the age of 2 years. Radiation dose was 4000 cGy to right orbit with lens shield. A chemotherapy regime which comprised actinomycin D, Adriamycin, cyclophosphamide, and vincristine, took 2 years. At the time of dental examination, she was 11 years 9 months old. Based on the scoring system by Demirjian and Goldstein (1976), her dental age was equal to a 10-year-old girl.
Figure 5-1  Panoramic radiograph showing delayed dental maturity (A) compared with that of normal age-matched child (B).
5.7 ABNORMALITIES OF THE DENTITION

In the present study, approximately two thirds of the study population is affected by a wide range of dental developmental abnormalities. Among the three different treatment groups, the head and neck irradiation group significantly gives the highest percentage of affected patients while the chemotherapy group has the lowest percentage. Furthermore, the distribution of the severity of dental disturbances is similar with the head and neck irradiation group having the greatest number of severe anomalies, then the cranial irradiation group, and, finally the chemotherapy group with the least.

In this study almost every patient received chemotherapy, although with differing regimens. The more severe dental disturbances for the head and neck irradiation group could be attributed to a higher radiation dose directly to, or near, the maxilla and mandible.

The prevalence of dental anomalies in survivors of childhood cancer varies in many previous studies. Jaffé et al (1984) found dental abnormalities in 82% of 45 patients treated with maxillofacial radiation. Fromm et al (1986), reported that eleven of 20 patients, receiving chemoradiotherapy for soft tissue sarcomas of head and neck showed some dental defects. The present result agrees with that of Maguire and co-workers (1987) who detected various dental abnormalities in 65% of 82 survivors of childhood malignancy. In the same year, Rosenberg and others (1987) noted that 13 out of 17 children who survived acute lymphoblastic leukaemia developed thinned roots and five had shortened roots. A quantitative analysis also disclosed a 63.33% to 84.38% reduction of premolar root length when compared with the mean of the historical controls.

Dahllöf and others (1988) reported impaired roots in 100% of 16 patients, having chemotherapy and total body irradiation. Using a computer linked planimeter, Pajari et al (1988b) found a significant reduction of the mean root area in children with anti-cancer
therapy, compared with the healthy controls. In 1990, Sonis and colleagues noted dental abnormalities in 94% of 97 survivors of childhood acute lymphoblastic leukaemia. Nunn et al (1991) detected dental defects in 46% of 52 patients, treated by chemotherapy with or without cranial irradiation.

There have been few studies that have compared dental anomalies between different treatments or cancer types. In 1984, Jaffe and others described a number of patients presenting dental abnormalities in different cancer diagnoses. They, however, did not establish a substantial difference between groups. A recent study (Näsman et al 1994) showed equal numbers of teeth affected by disturbances in enamel mineralisation between children receiving total body irradiation or chemotherapy only. The mean number of teeth with malformed roots in the total body irradiation group is, however, significantly higher than that of the chemotherapy group.

Overall, the present study reinforces those findings reported previously despite having variations in study design. Panoramic radiographs, used in all the above studies, appear to be a practical and reasonable tool for assessing dental defects in these patients. However, the accuracy and detail available from these radiographs are not universally standardised. Apart from using panoramic radiograph for subjective assessment, Rosenberg and others (1987) also conducted a quantitative assessment by using a parallel periapical radiograph technique. This technique, although more objective and accurate, requires more radiation exposure than required for the OPG. This can cause problems in that patients and their parents are very sensitive to requests for further radiation. Thus use of this technique can result in a reduction in the number of participating patients in a particular study.

Although this study also uses clinical and panoramic radiographic assessments that are comparable to the other major studies, the criteria for classifying defects does vary. In this study, despite the fact that the system used is subjective for assessing each individual tooth, it provides a simple and reliable method for grouping patients according to their
Discussion

degree of severity of dental abnormalities. It also facilitates comparison between particular findings and different, interesting variables. Prior to this, an accurate, quantifiable, and reproducible method for assessing and classifying oral complications of cancer therapy was not available.

In this study only one rater is responsible in evaluating radiographs. Although examiner reproducibility is high (92.6%), it does not preclude intra-rater biases. The use of multiple examiners in future may be appropriate to improve reliability and validity. In order to accomplish a consistent and standardised diagnoses of dental conditions, all examiners, however, need to be calibrated in advance. Then inter-examiner reliability should be assessed by using Pearson's correlation and Kappa statistics (Hunt 1986).

5.7.1 Number of Abnormal Teeth per Person

For the purposes of analysis, it was assumed that every patient potentially has 28 teeth. This study found that more than 25% of the total dentition of each patient (9-10 teeth) developed some dental defects. The number of altered teeth is significantly higher in the head and neck irradiation group and lowest in the chemotherapy group. These findings are consistent with the previously mentioned results, concerning the severity of dental anomalies.

While most previous studies observed the number of patients with dental anomalies, only two reported the number of affected teeth in each patient surviving childhood cancer. Pajari et al (1988c) detected significantly greater numbers of teeth with enamel opacities in patients after anti-neoplastic therapy, compared to the controls. In Sweden, similar results were also presented by Näsman et al (1994). The mean number of teeth with enamel disturbances in the chemotherapy group was 4.1 whilst in the BMT group it was 4.6. This was significantly higher than the healthy controls. They also showed greater mean numbers of teeth (15.9) with disturbances in root development in the BMT group, compared with the number of teeth (1.2) in the chemotherapy group. This is in line with the present finding. The mean number of altered teeth in the chemotherapy group in this
study is, however, obviously higher than that of Näsman et al (1994). They included only teeth with malformed roots. In contrast, this study takes all types of dental abnormalities into account. This explains the discrepancy in number of defective teeth.

5.7.2 Types of Dental Abnormalities

The present results showed that root shortening is the most common type of dental aberration in the total study population as well as in the three groups. Tapering of roots is the second most frequent defect, followed by microdontia, tooth agenesis, root agenesis, and taurodontia. The absence of teeth is more common for patients in the head and neck irradiation group, compared with those in the cranial irradiation and the chemotherapy groups. Root agenesis is also found only in the head and neck group.

These varying types of dental root abnormalities have also been detected in many previous studies (Welbury et al 1984, Fromm et al 1986, Maguire et al 1987, Rosenberg et al 1987, Pajari et al 1988, Dahllöf et al 1988, Sonis et al 1990, Nunn et al 1991, Násman et al 1994). The present results differ from the data of two previous studies (Sonis et al, 1990, Násman et al, 1994) in that they show that root shortening or V-shaped roots are found most frequently, compared with other defects. Maguire et al (1987) presented a large number of patients with abnormal root development, although the types of defects were not described.

The present findings generally indicate a higher prevalence of dental developmental abnormalities in the study population than would be expected in the normal population (excluding taurodontia). Although the figure for prevalence of missing teeth in this study is within the normal range of 10% to 25% (Stewart et al 1982), it should be noted that the third permanent molars are excluded from this study. Their inclusion would have raised the prevalence of missing teeth above the average. The prevalence of microdontia (30.6%) in this population is distinctly higher than that reported in the normal population (1.9% - 3.1%) Brook (1984). The variety of types of disturbances in root development is an unquestionably major complication of these patients.
5.7.3 Distribution Pattern of Dental Abnormalities

In this study, the distribution pattern of dental abnormalities in the total population is influenced by that in the cranial irradiation group, because of the large sample size for this group. Differing distribution patterns of dental abnormalities among three different treatment groups are revealed when separate investigations are conducted. For example, in the cranial irradiation group, the percentage of affected maxillary teeth ranges from low for the incisors, canines, premolars, to high for the molars. The percentage of affected teeth in the mandible appears highest in second permanent molars, followed by premolars, first permanent molars, canines, and incisors. This study also reveals that the maxillary teeth are significantly more affected (p<0.0001) than the mandibular teeth. The posterior teeth are altered more frequently (p<0.0001) than the anterior teeth.

This distribution pattern indicates the systemic effect of the chemotherapy regimen, which is augmented by local effect of cranial irradiation. From the mean age at diagnosis (4.2 years) in this group, it is possible to determine the stage that crowns of the first permanent molars and incisors were completely or almost completely calcified. The roots, however, are still developing. Also the permanent canines, premolars, and second permanent molars are calcifying. Thus any systemic disturbances during the next 2-3 years should involve the root formation of the first permanent molars and incisors and the crown and root development of the canines, premolars, and second permanent molars.

This pattern of disturbance due to the chemotherapy is complicated by the use of cranial irradiation. The relatively high position of the maxillary permanent posterior teeth in young children may place those teeth in the direct field of irradiation. As a result, the most frequently involved teeth are the maxillary molars and premolars. The mandibular permanent posterior teeth, although not in the direct irradiation field, certainly are exposed to some scattered doses of radiation. According to Chin (cited by Sonis et al 1990), it is estimated that teeth located along the edge of radiation field were exposed to approximately 45% of the administered dose. Furthermore, teeth which were, at a
maximum, 1 cm away from the edge of this field could have received 1% of this dose. Consequently, the mandibular posterior teeth, which were closer to the field, are more frequently affected than the mandibular anterior teeth. Less common defects in the mandibular first permanent molars, compared with that in the mandibular second permanent molars can be explained by a more mature stage of development of the former teeth at the time of treatment. The present study, although using a different method, obtains corresponding findings to those of Sonis et al (1990): Maguire et al (1987) also showed higher figures of dental anomalies in the maxillary teeth, compared with the mandibular teeth, in patients with acute lymphoblastic leukaemia.

In the head and neck irradiation group, there is no specific distribution pattern of dental abnormalities as mentioned above. Although the figures for affected teeth in the mandible are higher than those in the maxilla for many tooth types, there is no significant difference. The posterior teeth, however, are significantly altered more frequently than the anterior teeth (p<0.001).

The nonspecific distribution pattern of dental abnormalities in the head and neck irradiation group reflects various radiation fields and doses among the patients in this group. The finding, that the maxillary and the mandibular teeth are invariably altered, appears to be in line with figures shown by Maguire et al (1987).

The trend of more defects in the mandibular teeth is possibly due to irradiation to the submandibular region or neck. Approximately one quarter of patients being treated for lymphomas received such irradiation. Line et al (1979) found that the lateral scattered radiation from mantle field irradiation delivered a dose of approximately 400-1000 cGy to the tooth buds and mandibular growth centres. They concluded that scatter from mantle radiation field is significant to alter or retard development of the teeth and impair mandibular growth centres, even though not directly in the treatment field.
Discussion

Although a pattern of dental abnormalities for the chemotherapy group is not obvious, the first molars and first premolars seem to be equally affected, followed by the second molars, second premolars, and canines. With the exception of the maxillary lateral incisors, the incisors are the least altered tooth type in this group. As described in the head and neck irradiation group, there is a significant difference (p<0.0001) only between the posterior and anterior teeth and not between the maxillary and mandibular teeth.

The distribution pattern of dental abnormalities for the chemotherapy group suggests several underlying events. Firstly, the disturbance pattern corresponds to a chronological hypoplastic pattern. Secondly, there is a higher percentage of altered maxillary lateral incisors and premolars than found in the normal population possibly due to the chemotherapy regimen. The non-symmetrical pattern may possibly be due to differences in susceptibility to cytotoxic agents at varying developmental stages of the teeth.

5.7.4 Dental Abnormalities and the Age at Diagnosis

The present findings suggest that the patients who start cancer treatment with cranial irradiation or head and neck irradiation at less than 6 years of age, develop more severe dental abnormalities than those who commenced treatment at an older age. However, this did not apply to those children treated with chemotherapy alone.

The current result supports Dahllöf et al (1988) who reported the most severe and extensive dental aberrations in patients younger than 6 years of age at BMT. Similarly, Sonis et al (1990) found greater severity of dental abnormalities in children who received treatment for acute lymphoblastic leukaemia before the age of 5 years.

5.7.5 Dental Abnormalities and Radiation Dose

Concentrating on only the cranial irradiation group, the current study indicates that dental abnormalities occur more severely and extensively in patients who were treated with 2400-cGy radiotherapy, compared with those treated with 1800-cGy radiotherapy. This result confirms similar findings in the study by Sonis et al (1990).
5.7.6 Dental Abnormalities and Chemotherapeutic Protocol

These results include only patients from the cranial irradiation group. They reveal that patients, cured by LSA₂L₂ chemotherapeutic protocol, develop more severe dental aberrations than those, treated by BFM protocol.

This current study is the only work that associates dental abnormalities with cancer chemotherapeutic protocol. No previous clinical research reports have noted this, although there is a vast amount of literature concentrating on the effects of chemotherapeutic agents on dental development in animals. The adverse effects of cyclophosphamide, vinblastine, vincristine, doxorubicin, bleomycin, and 5-fluorouracil have been detailed (Rosenberg 1990). Both LSA₂L₂ and BFM protocols contain some of those above-mentioned agents (Appendix I). The severe effect of the LSA₂L₂ protocol over the BFM protocol is probably due to the different types of chemotherapeutic agents used. It may also be attributed to the higher radiation dose (2400-cGy), usually used with the LSA₂L₂ protocol. In the BFM protocol, this radiation dose is applied only to patients in high risk group (Appendix I).

5.7.7 Dental Abnormalities and Medical Complications

Growth hormone deficiency, learning difficulty, hypogonadism, and musculoskeletal disorders are common medical complications involving approximately one third of the study population. Complications, involving other systems, also occur to some degree. The distribution of the different types of complications varies among the three different treatment groups. Growth hormone deficiency, learning difficulty, and hypogonadism are dominant in the cranial irradiation and the head and neck irradiation groups, but not in the chemotherapy group. Musculoskeletal disorders are common in the head and neck irradiation and the chemotherapy groups.

The current study shows a significant association between severity of dental abnormalities and the presence of medical complications in 178 patients.
Discussion

There is only one study, by Fromm et al (1986), which focused not only on the late dental adversities but also on other treatment related complications. They reported a variety of late treatment related problems in 20 children with soft tissue sarcomas of the head and neck. The major problems encountered were related to the eyes (xerophthalmia and cataracts), ears (hearing loss), teeth (mal-eruption and caries), glandular structures (xerostomia, hypopituitarism), and development (craniofacial deformity). Although these complications were clearly described, a test to associate dental adversity to the other complications was not carried out.

Whether there is any true relationship between severity of dental abnormalities and medical complication needs to be explored further. The current findings, however, imply some meaningful issues for medical and dental personnel. The results from this study suggest that the damage to the developing dentition may be a valuable early warning sign for damage to other systems. That is, the signs of dental malformation are evident within several years of the commencement of treatment, and this information can be used to advise the supervising medical team of the likelihood that other more serious late effects could be present, or developing. For the teeth to be damaged, they would have received a significant insult which, if involving other more sensitive tissues, would cause similar or perhaps even greater disturbance. This relationship between the severity of dental damage and the ability to act as an early warning for significant damage to other more sensitive tissues around the body is one of the significant findings of this study.

In follow-up examinations of patients who survive childhood cancer, the medical team should be aware of the possible dental complications. The same consideration should also be of concern to a dentist in the management of these patients since several underlying medical complications may relate to dental treatment. Good collaboration between the medical and dental staff and within the dental profession is essential so that patients' existing problems can be ameliorated and further adversities can be minimised.
Discussion

In summary, the present results reinforce previous findings that dental developmental abnormalities exist as treatment-related consequences in survivors of childhood cancer. Types and severity vary upon cancer treatment and age at the commencement of therapy. Overall, the least severity is shown in the chemotherapy group, while the greatest is in the head and neck irradiation group. Children, younger than 6 years of age at the beginning of cancer treatment, develop more severe dental problems than the older children. In the cranial irradiation group, more severe dental abnormalities present in patients cured with 2400-cGy, and those treated by LSAcL2. Furthermore, the severity of dental anomalies is substantially associated with the presence of medical complications. As the patients' life expectancy becomes longer, these findings indicate that comprehensive dental management by a multidisciplinary team will be required.
CHAPTER SIX

CONCLUSIONS

The current report is an observational study. Two hundred and one long-term survivors of childhood cancer were reviewed at the Late Effects Clinic, Royal Alexandra Hospital for Children, Sydney. The large number of children in this study population enabled the classification of subjects into three major groups: viz. cranial irradiation; head and neck irradiation; and chemotherapy.

The present findings indicated that dental caries level and periodontal health of these patients, were within normal limits, and there was no difference in those variables between the three groups. Nevertheless, these patients deserve more attention from oral health carers due to evidence of other dental late effects which may predispose them to a greater susceptibility to oral diseases, early loss of teeth and associated complications.

The patients who received multi-agent chemotherapy plus radiation therapy to the head and neck region developed facial deformity and trismus more often than those treated successfully with chemotherapy plus cranial irradiation, or those treated with chemotherapy with or without radiotherapy to other parts of the body. These facial changes probably result from aggressive surgery and the high dosage of radiotherapy. It is, however, interesting that facial deformity was also present in the chemotherapy group. Facial alterations may lead to emotional and psychological consequences which may influence the effectiveness of all health education programs.

This study did not answer the question whether these patients have a higher prevalence of malocclusion than the normal population or not. The evidence of malocclusion and the need for orthodontic treatment, however, was noted in each group. Orthodontic
management in these patients can be more complicated. Other orofacial malformations should be considered in treatment planning and collaboration among many specialists may be required.

The effect of cancer therapy on dental maturity in the cranial irradiation group remains inconclusive, although there is a significant effect. The results add more information about a trend in retardation of dental maturity in the head and neck irradiation group. Future studies, using a more accurate assessing method than the method used in this study, are suggested to clearly identify this trend.

A new method for assessing and classifying dental developmental abnormality is introduced. It is feasible and enhances a possibility to describe and compare such problem among groups of patients with different characteristics.

The present findings confirm that dental developmental defects in these patients depend upon the age at commencement of cancer treatment and types of cancer therapy. The head and neck irradiation group had the most severe complications. The number of affected teeth per patient and pattern of dental abnormality in the three groups is described in detail.

This is the first report that relates dental abnormality to different chemotherapeutic treatment protocols and associates it to a presence of medical complications. This information is valuable for medical colleagues in assessment of cancer treatment and warns them to be aware of possible dental complications in these survivors. An impression that dental malformations may serve as a predictor of problems of other organs encourages future studies.
Conclusions

The current findings, although they can not answer all unsolved questions, do add more information about dental delayed complications in survivors of childhood cancer. Information, particularly about different outcomes from different types of treatment, is important feedback for oncology teams in evaluating their paediatric cancer therapy. The variety of dental problems should alert the dental profession to prepare itself for managing an increasing number of these patients in practice. In the future, adverse consequence of underlying complications may be prevented or minimised. Finally, curricula relevant to chronic dental complications of cancer therapy should be developed and implemented in schools of medicine, dentistry, and dental hygiene.
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APPENDICES

APPENDIX I  CANCER TREATMENT PROTOCOLS

The following is a summary of some treatment protocols for common childhood cancers used at the Royal Alexandra Hospital for Children.

Acute Lymphoblastic Leukaemia (ALL)

Protocols: Pinkel to 1976, LSA\textsubscript{L1} to 1982, BFM to 1985, then ANZCCSG Study V. Treated with the Pinkel protocol originally and then from 1976 to 1982 with the modified LSA\textsubscript{L2} (Memorial Sloan Kettering) therapy. Both of these involved 2400 rads cranial radiotherapy with 3-4 years of therapy in total. Since then a shorter (2 year) therapy has been given with reduced radiotherapy for all but high-risk patients.

ALL PROTOCOL - LSA\textsubscript{L2}
For patients diagnosed between 1975 and September 1982

INDUCTION

Intrathecal methotrexate (ITMTX)  \textit{day 1} - dose for age (see below)
Cyclophosphamide \hspace{1cm} 1200 mg/M\textsuperscript{2} IV \textit{day 1}
Prednisolone \hspace{1cm} 40 mg/M\textsuperscript{2}/day po \times 28 days, days 1-28
Vincristine \hspace{1cm} 1.5 mg/M\textsuperscript{2} IV days 4, 11, 18, 25
Daunomycin \hspace{1cm} 60 mg/M\textsuperscript{2} IV days 15, 16

CNS PROPHYLAXIS

Taper prednisolone to 0 over 7 days
Thioguanine \hspace{1cm} 75 mg/M\textsuperscript{2}/day po
Cranial irradiation 2400 R in 15 fractions
IT MTX 6 doses - 1st on day 1 of induction, remainder given twice weekly

<table>
<thead>
<tr>
<th>Dose MTX</th>
<th>Under 1 year:</th>
<th>6 mg</th>
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<tr>
<td></td>
<td>1 - 2 years</td>
<td>8 mg</td>
</tr>
<tr>
<td></td>
<td>2 - 3 years</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>over 3 years</td>
<td>12 mg</td>
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CONSOLIDATION

Cytosine \hspace{1cm} 150 mg/M\textsuperscript{2} IV or IM \times 15 doses
Thioguanine \hspace{1cm} 75 mg/M\textsuperscript{2} po 8-12 hrs after each Arabinoside-C
Asparaginase \hspace{1cm} 6000 \textmu M\textsuperscript{2} IM \times 12 doses
CCNU \hspace{1cm} 60 mg/M\textsuperscript{2} po
MAINTENANCE

Cycle 1: Thioguanine 300 mg/M2/day po x 4 days
Cyclophosphamide 100 mg/M2 IV day 5
9 days rest

Cycle 2: Hydroxyurea 2400 mg/M2/day po x 4 days
Daunomycin 40 mg/M2 IV or CPA 100 mg/M2 IV day 5
9 days rest

Cycle 3: Methotrexate 10 mg/M2/day po x 4 days
CCNU 60 mg/M2 po day 5
9 days rest

Cycle 4: Cytosine 150 mg/M2/day IV or IM x 4 days
Vincristine 1.5 mg/M2 IV (max. 2.0 mg) day 5
9 days rest

Cycle 5: IT MTX via LP day 1 (Dose for age - see above)
13 days rest then restart at Cycle 1
Cease Daunomycin after 480 mg/M2
Duration of therapy: Dx before Jan. 1979: 4 years
Dx. after Jan. 1980: 3 years

ALL PROTOCOL - BFM (PILOT)
For the treatment of newly diagnosed acute lymphoblastic leukaemia, from October 1982:

Standard risk group

INDUCTION

Phase I
IT MTX day 1 dose: see below
Prednisolone 60 mg/M2/day x 28 days
Vincristine 1.5 mg/M2 (max. 2.5 mg) IV days 1, 8, 15, 22
Daunomycin 30 mg/M2 IV days 1, 8, 15, 22
L-asparaginase 6,000 units/M2 IM x 9 (M, W, F comm. day 3 or 4).
Rest period 14 days, BMA

Phase II (neutrophils 250, platelets 100,000/cu mm)
Cyclophosphamide 1000 mg/M2 IV x 2, day 1 and 28
(day 28 dose: neutrophils 100, platelets 50,000/cu mm)
Mercaptopurine 60 mg/M2/day x 28 days (WCC 600/cu mm)
Cytosine 75 mg/M2/day IV x 4 days, days 3-6, 10-13, 17-20, and 24-27
(neutrophils 100, platelets 50,000/cu mm)
IT MTX - 4 doses, on days 3, 10, 17 and 24
Dose per age: under 1 yr: 6 mg
1-2 yr: 8 mg
2-3 yr: 10 mg
over 3 yr: 12 mg
Cranial radiotherapy if age over 2 years. Dose 1800 R in 10-15 fractions over 2-3 weeks
Give later if under 2
Rest period 14 days
INTERVAL MAINTENANCE (neutrophils 750, platelets 100,000/cu mm)

Mercaptopurine  50 mg/M²/day (WCC 1500-3500/cu mm)
Methotrexate    20 mg/M²/week
Duration 8 weeks
Rest period 14 days

REINDUCTION - STANDARD RISK GROUP (neutrophils 1000, platelets 100,000/cu mm)

BMA before starting
Dexamethasone   10 mg/M²/day x 14 days, taper to 0 over 7 days
Vinblastine     1.5 mg/M² IV (max. 2.0 mg) days 1, 8
Adriamycin      30 mg/M² IV days 1, 8
Rest 7 days
Thioguanine     60 mg/M²/day x 14 days
Cytosine        75 mg/M²/day IV daily x 4 days, days 15-18, 22-25
(neutrophils 100, platelets 50,000/cu mm)
IT MTX x 2, on days 15 and 22. Dose for age (see above)
Rest 14 days

FINAL MAINTENANCE (neutrophils 750, platelets 100,000/cu mm)

Mercaptopurine  75 mg/M²/day (WCC 1500-3500/cu mm)
Methotrexate    20 mg/M²/week
Duration - to end of 2nd year

ALL PROTOCOL - BFM (PILOT)

Middle risk group

INDUCTION

Phase I
IT MTX day 1 dose: see below
Prednisolone    60 mg/M²/day x 28 days
Vinblastine     1.5 mg/M² (max. 2.5 mg) IV days 1, 8, 15, 22
Daunomycin      30 mg/M² IV days 1, 8, 15, 22
L-asparaginase   6,000 units/M² IM x 9 (M, W, F comm. day 3 or 4)
Rest period 14 days, BMA

Phase II (neutrophils 250, platelets 100,000/cu mm)
Cyclophosphamide 1000mg/M² IV x 2, day 1 and 28
(day 28 dose: neutrophils 100, platelets 50,000/cu mm)
Mercaptopurine  60 mg/M²/day x 28 days (WCC 600/cu mm)
Cytosine        75 mg/M²/day IV x 4 days, days 3-6, 10-13, 17-20, and 24-27
(neutrophils 100, platelets 50,000/cu mm)
IT MTX - 4 doses, on days 3, 10, 17 and 24
Dose per age: under 1 yr: 6 mg
              1-2 yr: 8 mg
              2-3 yr: 10 mg
              over 3 yr: 12 mg
Cranial radiotherapy if age over 2 years. Dose 1800 R in 10-15 fractions over 2-3 weeks
Give later if under 2
Rest period 14 days

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INTERVAL MAINTENANCE (neutrophils 750, platelets 100,000/cu mm)

Mercaptopurine  50 mg/M2/day (WCC 1500-3500/cu mm)
Methotrexate   20 mg/M2/week
Duration 8 weeks
Rest period 14 days

REINDUCTION - MIDDLE RISK GROUP (neutrophils 1000, platelets 100,000/cu mm)
BMA before starting

Phase I
Dexamethasone  10 mg/M2/day x 28 days, taper to zero over 7 days
Vincristine    1.5 mg/M2 IV (max. 2.0 mg) days 1, 8, 15, 22
Adriamycin     30 mg/M2 IV days 1, 8, 15, 22
L-asparaginase 10,000 units/M2 IMI days 1, 4, 8, 11
Rest 14 days

Phase II (neutrophils 250, platelets 100,000/cu mm)
Cyclophosphamide:1000 mg/M2 IV day 1
Thioguanine    60 mg/M2/day x 14 days (WCC 600/cu mm)
Cytosine       75 mg/M2/day IV daily x 4 days, days 3-6, 10-13
(neutrophils 100, platelets 50,000/cu mm)
IT MTX x 2, on days 3 and 10  Dose for age (see above)
Rest 14 days

FINAL MAINTENANCE (neutrophils 750, platelets 100,000/cu mm)

Mercaptopurine  75 mg/M2/day (WCC 1500-3500/cu mm)
Methotrexate   20 mg/M2/week
Duration - to end of 2nd year

ALL PROTOCOL - BFM (PILOT)

High risk group

INDUCTION

Phase I
IT MTX day 1 dose: see below
Prednisolone   60 mg/M2/day x 28 days
Vincristine    1.5 mg/M2 (max. 2.5 mg) IV days 1, 8, 15, 22
Daunomycin     30 mg/M2 IV days 1, 8, 15, 22
L-asparaginase 6,000 units/M2 IMI x 9 (M, W, F comm. day 3 or 4)
Rest period 14 days, BMA

Phase II (neutrophils 250, platelets 100,000/cu mm)

Cyclophosphamide 1000mg/M2 IV x 2, day 1 and 28
(day 28 dose: neutrophils 100, platelets 50,000/cu mm)
Mercaptopurine  60 mg/M2/day x 28 days (WCC 600/cu mm)
Cytosine        75 mg/M2/day IV x 4 days, days 3-6, 10-13, 17-20, and 24-27
(neutrophils 100, platelets 50,000/cu mm)
Appendices

IT MTX - 4 doses, on days 3, 10, 17 and 24

Dose per age:
- under 1 yr: 6 mg
- 1-2 yr: 8 mg
- 2-3 yr: 10 mg
- over 3 yr: 12 mg

Cranial radiotherapy if age over 2 years. Dose **2400 R** in 10-15 fractions over 2-3 weeks.

Give later if under 2.

Rest period 14 days

**INTERVAL MAINTENANCE** (neutrophils 750, platelets 100,000/cu mm)

Mercaptopurine 50 mg/M2/day (WCC 1500-3500/cu mm)

Methotrexate 20 mg/M2/week

Duration 8 weeks

Rest period 14 days

**REINDUCTION - high risk group** (neutrophils 1000, platelets 100,000/cu mm)

BMA before starting

**Phase I**

VM-26 165 mg/M2 IV & cytosine 300 mg/M2 IV days 1, 4, 8, 11

Optional rest if required

**Phase II** (neutrophils 200, platelets 50,000/cu mm)

Dexamethasone 10 mg/M2/day x 28 days, taper to zero over 7 days

Vincristine 1.5 mg/M2 IV (max. 2.0 mg) days 1, 8, 15, 22

Adriamycin 30 mg/M2 IV days 1, 8, 15, 22

Rest 14 days

**Phase III**

Thioguanine 60 mg/M2/day x 14 days

Cytosine 75 mg/M2/day IV daily x 4 days, days 3-6, 10-13

(neutrophils 100, platelets 50,000/cu mm)

IT MTX x 2, on days 3 and 10. Dose for age (see above)

Rest 14 days

**FINAL MAINTENANCE** (neutrophils 750, platelets 100,000/cu mm)

Mercaptopurine 75 mg/M2/day (WCC 1500-3500/cu mm)

Methotrexate 20 mg/M2/week

Duration - to end of 2nd year
DEFINITION OF RISK FACTORS AND SUBGROUPS FOR STUDY V

Group I

Very Favourable Prognosis ALL
Age 2-9 years (24-119 months inclusive) and WBC < 10,000
excluding:

- > 10% FAB L2 marrow blasts
- Boys with < 100,000 platelets/ul
- Lymphoma-leukaemia

# Chromosomes

Group II

Average Risk ALL
Age 1 year (12-23 months) and WBC < 50,000
or Age 2-9 years (24-119 months)
and WBC < 10,000
and either > 10% L2 blasts
or boys with < 100,000 platelets/ul

or Age 2-9 years (24-119 months)
and WBC 10,000 - 50,000

or Age 10-20 years (120-251 months)
and WBC < 50,000
excluding:

- > 10% FAB L2 marrow blasts
- Lymphoma-leukaemia

High Risk ALL
Age 1-20 years (12-251 months)
and either WBC ≥ 50,000
or Average Risk ALL on Age and WBC
but excluding Lymphoma-leukaemia

Lymphoma-ALL
Age 1-20 years (12-251 months)
and at least 1 physical finding
plus at least 1 laboratory finding:

Physical Finding
Massive lymphadenopathy
Massive splenomegaly
Large anterior mediastinal mass

Laboratory Finding
≥ 25% T cells
Haemoglobin ≥ 10 Gm/dl
WBC ≥ 50,000

(Note that the FAB blast percentage of > 10% L2 blasts raises the risk classification by one subgroup only.)

# Patients who by standard criteria have a very favourable prognosis but who have chromosome findings predictive of a poor prognosis viz translocation may be removed from this group and treated more intensively.
### Appendices

**ALL PROTOCOL - ACCSG -V**

**Group I (low risk)**

**INDUCTION (5 weeks)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
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<tbody>
<tr>
<td>Vincristine</td>
<td>1.5mg/M² (max. dose 2.0mg) IV, days 1, 8, 15, 22.</td>
</tr>
<tr>
<td>Daunomycin</td>
<td>25mg/M² IV, days 1, 8, 15, 22</td>
</tr>
<tr>
<td>L-asparaginase</td>
<td>6,000U/M² IM x 9 (Mon, Wed, Fri commencing day 3 or 4)</td>
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<tr>
<td>Prednisolone</td>
<td>40mg/M²/day for 28 days in 3 divided doses. Taper to 0 over 7 days</td>
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<tr>
<td>IT methotrexate</td>
<td>Days 2, 22 in age related doses</td>
</tr>
<tr>
<td></td>
<td>Doses: 1-2 years: 8 mg</td>
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<tr>
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<td>2-3 years: 10 mg</td>
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<td>&gt; 3 years: 12 mg</td>
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</table>

BMA - day 36
Day 36 becomes day 1 of CNS prophylaxis.

**CNS PROPHYLAXIS (4 weeks) (neutrophils > 1 x 10⁹/L; platelets > 100 x 10⁹/L)**

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<td>Days 1, 8, 15, 22 in age-related doses</td>
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</table>

Day 29 becomes day 1 of maintenance.

**MAINTENANCE (12 x 8 week cycles = 96 weeks)**
(Neutrophils >1 x 10⁹/L, platelets > 100 x 10⁹/L)

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<th>Drug</th>
<th>Dosage Details</th>
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<td>Vincristine</td>
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<td>Mercaptopurine</td>
<td>75 mg/M²/day orally, days 1-42</td>
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<td>Methotrexate</td>
<td>30 mg/M²/week, days 2, 9, 16, 23, 30, 37</td>
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<td>IT MTX</td>
<td>(Start with 2nd cycle/deduct IT MTX dose from day 2 oral mtx/age-related doses)</td>
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<td>Two weeks rest (days 42-56)</td>
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<tr>
<td>Day 57</td>
<td>becomes day 1 of next cycle.</td>
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</tbody>
</table>
ALL PROTOCOL - ACCSG - V

Average and group II (high risk)

INDUCTION (5 Weeks)

- Vincristine 1.5mg/M² (max. dose 2.0mg) IV, days 1, 8, 15, 22.
- Daunomycin 25mg/M² IV, days 1, 8, 15, 22
- L-asparaginase 6,000U/M² IM x 9 (Mon, Wed, Fri commencing day 3 or 4)
- Prednisolone 40mg/M²/day for 28 days in 3 divided doses. Taper to 0 over 7 days
- IT Methotrexate Days 2, 22 in age related doses
  Doses: 1-2 years: 8mg
          2-3 years: 10mg
          > 3 years: 12 mg

BMA - day 36
Day 36 becomes day 1 of CNS prophylaxis

CNS PROPHYLAXIS - CONSOLIDATION (neutrophils > 0.5 x 10^9/L, platelets > 100 x 10^9/L)

- Irradiation 1800 rads
- IT MTX Days 1, 8, 15, 22 in age-related doses
- Vincristine 1.5 mg/M² IV (max. 2.0mg), days 1, 8, 22, 29
- ARA-C 75 mg/M²/day IV or S.C., days 1-4, 8-11, 22-25, 29-32
- Cyclophosphamide 1,000 mg/M² IV, days 1 and 22
  (admit for 24 hours double maintenance)
  First 14 days to be modified only for sepsis
  Rest until day 43
  Day 43 becomes day 1 of Phase I maintenance.

ARM A MAINTENANCE

Phase I: L-Asparaginase intensification
(neutrophils >1 x 10^9/L; platelets > 100 x 10^9/L)

- L-asparaginase 25,000U/M² IM (max. 40,000U) weekly for 20 doses
  Must be before MTX
- Mercaptopurine 50mg/M²/day for 14 days commencing day after L-asparaginase, then
  7 days off
  This 3 week cycle (14 days on, 7 days off) is repeated until
  L-asparaginase completed.
  Methotrexate 15mg/M², days 1 and 8 of each 2 week pulse of 6MP until
  L-asparaginase completed
  Rest for 2 weeks

Phase II: Intermittent maintenance (9 cycles x 5 weeks = 72 weeks)
(Neutrophils >1 x 10^9/L; platelets > 100 x 10^9/L)

- Vincristine 1.5mg/M² IV (max. 2.0mg), days 1, 29
- Mercaptopurine 75mg/M²/day, days 1-42
- Methotrexate 30mg/M²/day, days 2, 9, 16, 23, 30, 37
  Rest days 43-56
  Day 57 becomes day 1 of next cycle.

201
ARM C MAINTENANCE (BFM - cyclic maintenance)
(Neutrophils > 1 x 10^9/L; platelets > 100 x 10^9/L)

Phase I: Interim maintenance (6 weeks)
Mercaptopurine 50mg/M^2/day, days 1-42
Methotrexate 15mg/M^2, days 2, 9, 16, 23, 30, 37
Rest two weeks (Days 43-56)
Day 57 becomes day 1 of next phase.

Phase II: Reinduction (4 weeks)
(Neutrophils > 1 x 10^9/L; platelets > 100 x 10^9/L)
Vincristine 1.5 mg/M^2 IV, days 1, 8, 15, 22
Adriamycin 25 mg/M^2 IV, days 1, 8, 15, 22
Dexamethasone 6 mg/M^2 orally, days 1-22, then taper to zero over seven days
L-asparaginase 6,000U/M^2 IM x 6 doses (Mon, Wed, Fri commencing day 1)
Rest days 29-35

Phase III: Reconsolidation (3 weeks)
(Neutrophils > 1 x 10^9/L; platelets > 100 x 10^9/L)
Cyclophosphamide 1,000 mg/M^2 IV, day 36. Admit for 24 hours double maintenance fluids
6 Thioguanine 60 mg/M^2/day orally, days 36-50
ARA-C 75 mg/M^2 IV or S.C., days 36-39, 43-56
Rest for two weeks (Days 51-63)
Day 64 becomes day 1 of Phase IV.

Phase IV: Cyclic maintenance (9 x 8 week cycles)
Block I (Cycles 1-5)

Week 1
Vincristine 1.5mg/M^2 IV (max. 2.0mg), day 1
Daunomycin 40mg/M^2, day 1
Mercaptopurine 225mg/M^2 orally, days 1-5
Prednisolone 40mg/M^2 orally, days 1-5

Week 2
Rest

Week 3
Methotrexate 7.5mg/M^2 orally, days 1-5
Mercaptopurine 225mg/M^2 orally, days 1-5

Week 4
Rest

Week 5
Cyclophosphamide 600mg/M^2 IV, day 1. (Admit for 6 hours 2 x IVF)
Vincristine 1.5mg/M^2 (max. 2.0mg), day 1
Mercaptopurine 225mg/M^2 orally, days 1-5
Prednisolone 40mg/M^2 orally, days 1-5

Week 6
Rest

Week 7
Repeat Week 3

Week 8
Rest

Week 9
Start at Week 1

Block II (Cycles 6-9)
After 5 cycles, Daunomycin is omitted from Week 1 and replaced with Methotrexate 7.5mg/M^2 orally, days 1-5 for last 4 cycles.
ALL PROTOCOL - PINKEL (modified)

PROTOCOL: Initial therapy for patients with
... lymphoblast count less than 20,000/mm³
... hepatomegaly and/or splenomegaly less than 5cm below costal margin
... no mediastinal mass
... "null cell" leukaemia.

SOURCE: U.S. Children's Cancer Study Group A
ACTIVATED: October, 1975.
OUTLINE: Induction
Vincristine IV 1.5mg/M2/week x y,
Prednisone oral, 40mg/M2/day x 28 days,
taper over 14 days.

Sanctuary Treatment
Cranial irradiation 2400 rads
Methotrexate IT 12mg/M2 twice a week x six doses
6-mercaptopurine 75mg/M2/day, orally

Maintenance
6-Mercaptopurine 75mg/M2/day, orally
Methotrexate 20mg/M2/week, orally
Every six weeks, pulse doses of:
Vincristine 1.5mg/M2 x 1. IV
Prednisone 40mg/M2/day x 5 days, orally
Stop treatment after three years of maintenance therapy

NON-HODGKIN'S LYMPHOMA PROTOCOL - ACCSG

Stage I - II

INDUCTION
Vincristine 1.5 mg/M2 (max. 2.0 mg) IV days 1, 8, 15, 22
Cyclophosphamide 1000 mg/M2 IV days 1, 22 and 43
Prednisolone 50 mg/M2/day po x 28 days then taper
IT MTX days 1, 22 and 43:
Dose Under 1 year: 6 mg
1 - 2 years: 8 mg
2 - 3 years: 10 mg
Over 3 years: 12 mg
Rest 3 weeks

CNS PROPHYLAXIS (head and neck primaries only)

IT MTX as indicated above

MAINTENANCE
Vincristine 1.5 mg/M2 (max. 2.0 mg) day 1 and 29
Mercaptopurine 75 mg/M2? day po days 1 - 43
Methotrexate 30 mg/M2/week po days 1, 8, 15, 22, 29, 36
Rest days 43 - 47
Repeat for 5 cycles then stop
Stage III - IV

INDUCTION (Weeks 1 - 12)

Cyclophosphamide 1000 mg/M2 IV days 1, 50
Adriamycin 50 mg/M2 IV days 1, 50
Vincristine 1.5 mg/M2 (max. 2.0 mg) IV days 1, 8, 15, 22
Prednisolone 100 mg/M2/day po x 5 days, days 1-5 and 50-55
IT MTX day 1, 50

Alternating with

Cyclophosphamide 40 mg/M2/dose IV 8th hourly x 12 doses days 22-24, 71-73
Cytosine 40 mg/M2/dose IV 8th hourly x 12 doses days 22-24, 71-73
L-asparaginase 10,000 u./M2/day IM x 4 doses, days 25 - 28, 74 - 77
IT MTX day 22, 71.
Rest weeks 12 - 14.

CNS PROPHYLAXIS (Week 15)

Cyclophosphamide 1000 mg/M2 IV day 1
Vincristine 1.5 mg/M2 (max. 2.0 mg) IV day 1
Prednisolone 100 mg/M2/day po x 5 days
Cranial XRT 2400 R (omit Stage III Abdominal)
IT MTX weekly x 4 doses.
Rest 2 weeks.

MAINTENANCE

WEEK 20-21 VM-26 165 mg/M2 & cytosine 300 mg/M2 IV x 4 doses over 2 weeks
Week 22-24 Rest
WEEK 25 Cyclophosphamide 750 mg/M2 IV day 1
      Adriamycin 50 mg/M2 IV day 1
      Vincristine 1.5 mg/M2 (max. 2.0 mg) day 1
      Prednisolone 100 mg/M2/day po x 5 days
Week 26-28 Rest
WEEK 29-30 Repeat Week 20-21 (VM-26)
Week 31-33 Rest
WEEK 34 Repeat Week 25 (CHOP)
Week 35-37 Rest
WEEK 38-39 Repeat Week 20-21 (VM-26)
Week 40-42 Rest
WEEK 43 Repeat Week 25 (CHOP)
Week 44-46 Rest
WEEK 47 Repeat Week 25 (CHOP)
Week 48-50 Rest
WEEK 51 Repeat Week 25 (CHOP)
Week 52-54 Rest
WEEK 55 Repeat Week 25 (CHOP) then cease treatment
Duration of therapy 13 months
APPENDIX II  EVALUATION OF DENTAL DEVELOPMENT-
DENTAL AGE- DEMIRJIAN SYSTEM

Assigning the Ratings

1. The mandibular permanent teeth are rated in the following order:
2nd molar, 1st molar, 2nd bicuspid, 1st bicuspid, canine, lateral incisor, central incisor.

2. All teeth are rated on a scale A to H. The rating is assigned by following carefully the
written criteria for each stage, and by comparing the tooth with the diagrams and X-ray
pictures given in Figure II. The illustrations should only be used as an aid, not as the sole
source of comparison. For each stage there are one, two or three written criteria marked
a), b), c). If only one criterion is given this must be met for the stage to be taken as
reached; if two criteria are given, then it is sufficient if the first one of them is met for the
stage to be recorded as reached; if three criteria are given, the first two of them must be met
for the stage to be considered reached. At each stage, in addition to the criteria for that
stage, the criteria for the previous stage must be satisfied. In borderline cases the earlier
stage is always assigned.

3. There are no absolute measurements to be taken. A pair of dividers is sufficient to compare
the relative length (crown/root). To determine apex closure stages no magnifying glass is
necessary. The ratings should be made with the naked eye.

4. The crown height is defined as being the maximum distance between the highest tip of the
cusps and the cementoenamel junction. When the buccal and lingual cusps are not at the
same level, the midpoint between them is considered as the highest point.

Using the Scoring System

1. Each tooth will have a rating, assessed by the procedure already described.

2. This is converted into a score using Table II-A for males and females as appropriate. For
example, if tooth M₁ is in stage E it is given a score 7.5 for males and 5.6 for females.

3. The scores for all seven teeth are added together giving a total score. This is called the
dental maturity score.

4. The dental maturity score may then be plotted on the centile charts (males or females as
appropriate) where the age of the child is known. For example, a score of 72 for a male
aged 9.0 years lies just above the 10th centile.

5. The maturity score may be converted directly into a dental age either by reading off on the
horizontal scale the age at which the 50th centile attains that maturity score value, or by
using Tables II-B or II-C which have been constructed for this purpose. Thus a score of
45.2 for a male is equivalent to a dental age of 6.3 years.
Dental Formation Stages

If there is no sign of calcification, the rating 0 is given. The crypt formation is not taken into consideration.

STAGE DESCRIPTION

A In both uniradicular and multiradicular teeth, a beginning of calcification is seen at the superior level of the crypt in the form of an inverted cone or cones. There is no fusion of these calcified points.

B Fusion of the calcified points forms one or several cusps which unite to give a regularly outline occlusal surface.

C a. Enamel formation is complete at the occlusal surface. Its extension and convergence towards the cervical region is seen.
b. The beginning of a dentinal deposit is seen.
c. The outline of the pulp chamber has a curved shape at the occlusal border.

D a. The crown formation is completed down to the cementoenamel junction.
b. The superior border of the pulp chamber in the uniradicular teeth has a definite curved form, being concave towards the cervical region. The projection of the pulp horns if present, gives an outline shaped like an umbrella top. In molars the pulp chamber has a trapezoidal form.
c. Beginning of root formation is seen in the form of a spicule.

E Uniradicular teeth:
a. The walls of the pulp chamber now form straight lines, whose continuity is broken by the presence of the pulp horn, which is larger than in the previous stage.
b. The root length is less than the crown height.

Molars:
a. Initial formation of the radicular bifurcation is seen in the form of either a calcified point or a semi-lunar shape.
b. The root length is still less than the crown height.

F Uniradicular teeth:
a. The walls of the pulp chamber now form a more or less isosceles triangle. The apex ends in a funnel shape.
b. The root length is equal to or greater than the crown height.

Molars:
a. The calcified region of the bifurcation has developed further down from its semi-lunar stage to give the roots a more definite and distinct outline with funnel shaped endings.
b. The root length is equal to or greater than the crown height.

G a. The walls of the root canal are now parallel and its apical end is still partially open (Distal root in molars).

H a. The apical end of the root canal is completely closed (Distal root in molars).
b. The periodontal membrane has a uniform width around the root and the apex.
Figure II  Radiograph and diagram used in rating dental formation stages
Table II-A  Self-weighted scores for dental stages
7 teeth (Mandibular left side)

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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
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## Table II-B  Scores of dental maturity (7 teeth)

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### APPENDIX III

**AVERAGE MEASUREMENTS OF PERMANENT EXTRACTED TEETH**
(Source: Woelfel, 1990)

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| Lateral incisor (234) | 9.4 | 13.5 | 1.43 | 22.1 | 5.7 | 3.8 | 6.1 | 5.8 | 2.1 | 1.5 |
| Canine (316) | 11.0 | 15.9 | 1.45 | 25.9 | 6.8 | 5.2 | 7.7 | 7.5 | 2.4 | 1.6 |
| First premolar (228) | 8.8 | 14.4 | 1.64 | 22.4 | 7.0 | 4.8 | 7.7 | 7.0 | 0.9 | 0.6 |
| Second premolar (227) | 8.2 | 14.7 | 1.80 | 22.1 | 7.1 | 5.0 | 8.2 | 7.3 | 0.8 | 0.5 |
| First molar (231) | 7.7 M | 14.0 | 1.83 | 20.9 | 11.4 | 9.2 | 10.2 | 9.0 | 0.5 | 0.2 |
| | D | 13.0 | | | | | | | | |
| Second molar (236) | 7.7 M | 13.9 | 1.82 | 20.6 | 10.8 | 9.1 | 9.9 | 8.8 | 0.5 | 0.2 |
| | D | 13.0 | | | | | | | | |
| Third molar (252) | 7.5 M | 11.8 | 1.57 | 18.2 | 11.3 | 9.2 | 10.1 | 8.9 | 0.4 | 0.2 |
| | D | 10.8 | | | | | | | | |
| Avg. 2180 Lower teeth | 8.62 | 13.85 | 1.62 | 21.61 | 8.17 | 6.24 | 8.22 | 7.44 | 1.20 | 0.80 |