RADIATION MODALITIES IN THE TREATMENT OF NEUROBLASTOMA

Essay

Submitted for partial fulfilment of M.Sc. degree in

Radiotherapy and Nuclear medicine

By

HODA MAHMOUD KAMEL AL-BOOZ

(MB, Bch.)

Ain Shams University

Under supervision of

PROF. LAILA FARIS MATTA,
Head of the Radiotherapy and Nuclear medicine Department,
Faculty of Medicine,
Ain Shams University.

DR. TOM E. WHELDON,
Top Scientist and Senior Lecturer,
Radiation Oncology Department,
CRC Beatson Laboratory,
Glasgow University,
U.K.

DR. AMIN E. A. AMIN,
Lecturer in Radiation Physics,
Radiotherapy and Nuclear Medicine Department,
Faculty of Medicine,
Ain Shams University.

Faculty of Medicine

Ain Shams University

Cairo-Egypt

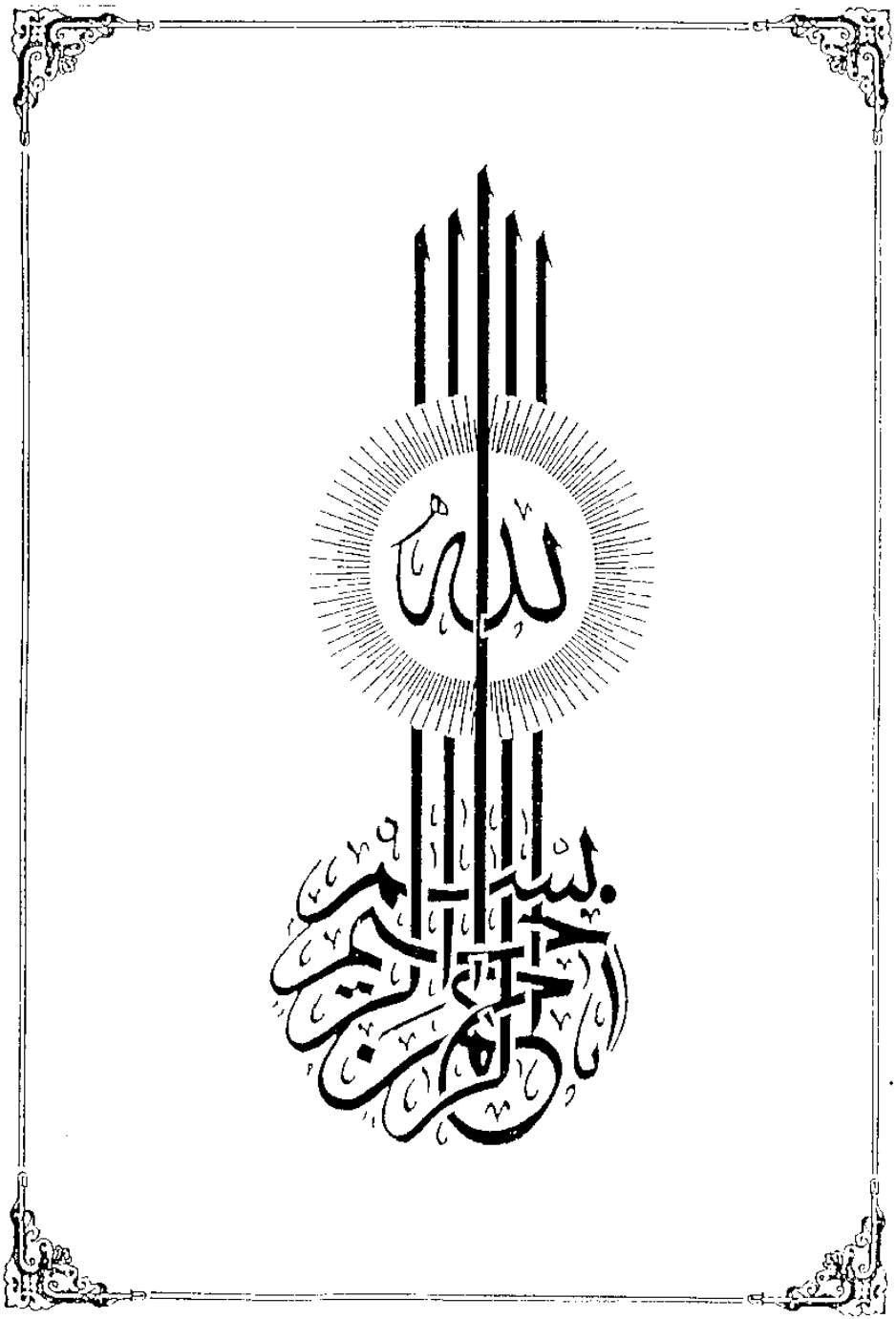
1994

بسم الله الرحمن الرحيم

"وإذا مَـرِضْـتُ فَهُـوَ يَشْفِـــين"

صدق الله العظيم

[٨٠ - الشعراء]



حديث شريف

"أَذْهِبِ البَأسَ ربَّ الناس،
اشفِ وأنتَ الشَّافِـــى،
لاشِفَاءَ إلا شـــفاؤُك،
شِفاءً لايغادر سَقَماً"

رواه البخاري

ACKNOWLEDGMENT

"Thank you GOD for helping me to complete this work"

I wish to express my deepest gratitude and appreciation to **Prof. Laila Faris,** Professor of Radiotherapy and Nuclear Medicine, Ain-Shams University, to whom I am deeply grateful for her help and supervision to complete this essay.

I was impressed by the kindness and the help of **Prof. Ann Barrett,** Professor of Radiotherapy, Beatson Oncology Center, Western Infirmary Hospital, Glasgow, who meticulously revised this work, and provided me with profitable advice and valuable suggestions.

I feel a great honour for being supervised by **Dr. Tom Wheldon,** Top scientist and Lecturer, Radiation Oncology Department, CRC Beatson Laboratory, Glasgow University. He provided me with constant supervision and best knowledge to perform this work. He generously offered me his time, effort and very wide experience to revise all the details of this work.

I was fortunate enough to have **Dr. Amin E. Amin,** Lecturer of Radiation Physics, Radiotherapy and Nuclear Medicine Department, Ain-Shams University, for some time in Glasgow at the time I was working on this essay. Many thanks are devoted to him for his sincere help and valuable advice.

My deepest appreciation goes to all **senior staff** of Radiotherapy and Nuclear Medicine Department, Ain-Shams University for allowing me to spend some time training at the Beatson Oncology Center, Glasgow.

Contents

Figures

Tables

List of Abbreviations

BMR	:	Bone Marrow Rescue
BMT	:	Bone Marrow Transplantation
CAA	:	Catecholacetic acid
Ci	:	Curie 1 mCi = 37 MBq
cGY	:	centi Gray
CT	:	Computerized Tomography
CXR	:	Chest X-ray
DA	:	Dopamine
EGF	:	Epidermal Growth Factor
HVA	:	Homovanillic acid
ISS	:	International Staging System
IVP	:	Intravenous Pyelogram
MBq	:	Mega Bequerel
mIBG	:	meta- iodo-benzyl-guanidine
MN	:	Metanephrine
MRI	:	Magnetic Resonant Imaging
3MT	:	3 Methoxytyramine
myc	:	A gene found in avian myelocytomatosis
NGF	:	Nerve Growth Factor
NMN	:	Normetanephrine
NSE	:	Neurone Specific Enolase
POG	:	Paediatric Oncology Group
TBI	:	Total Body Irradiation
TGF	:	Tissue Growth Factor
TNM	:	Tumour classification according to tumour size, regional lymph nodes, and distant metastases.

UICC	:	International union against cancer
UK	:	United Kingdom
UKCCSG	:	United Kingdom Children's Cancer Study Group
USA	:	United States of America
VAA	:	Vanilacetic acid
VMA	:	Vanillylmandellic acid

****

INTRODUCTION

INTRODUCTION

Neuroblastoma is one of the most common malignancies in children. The tumour is derived from cells of the sympathetic nervous system and the malignant cells may retain some features characteristic of this cell type. Though early stage disease, and even advanced disease in infants has a good prognosis, most patients present with stage 3 or 4 disease for which the outlook is very poor. Prognostic variables apart from stage include age, implication of the N-*myc* oncogene, abnormalities of chromosome 1 and DNA content (ploidy) of the tumour cells (chapter1.3.2). More effective treatments are required for patients with poor prognostic features. Currently, neuroblastoma treatment includes surgery and combination chemotherapy with a variety of agents. The development of drug resistance may be a problem. The use of bone marrow rescue to allow high intensity chemotherapy (e.g. with high dose melphalan) is being explored. Radiotherapy is not at present the major form of treatment in most cases of neuroblastoma, but new possibilities are developing for innovative use of radiation modalities of several kinds in the treatment of neuroblastoma. This work is concerned with new possibilities for radiation in neuroblastoma therapy.

EXTERNAL BEAM IRRADIATION

Currently, radiotherapy (external beam fractionated) may be employed to achieve local control of tumour masses. Since neuroblastoma is a radiosensitive neoplasm, the treatment doses need not be as high as in some other radiotherapy regimes but therapeutic radiation doses always carry risks of developmental abnormalities in growing children. It is not yet completely clear whether the radiobiology of developing tissues and organs is identical to that of steady-state renewal tissues in the adult. It is also not certain whether new strategies of fractionation

(hyperfractionation, acceleration) will be therapeutically beneficial in neuroblastoma or not. Since neuroblastoma is a rapidly metastasising tumour (i.e. often a systemic malignancy), attempts have been to use whole body irradiation (TBI), together with bone marrow rescue (autologous or syngenic) to eradicate micrometastases throughout the body (chapter2.4). The success of this strategy is not yet completely known. However, radiobiological calculations have suggested that the TBI strategy could fail in some patients because large micrometastases (e.g. 1 mm diameter) are too large for eradication by the TBI dose given (usually < 14 Gy) but that these tumours are not yet large enough to be detectable by imaging and therefore cannot be treated by high dose localized radiotherapy using small fields (chapter 2.3). Some improvements in the treatment of neuroblastoma by radiotherapy are therefore required.

TARGETED RADIOTHERAPY

One of the new possibilities for treatment of neuroblastoma by radiation is targeted radiotherapy using meta-iodo-benzyl-guanidine (mIBG) as targeting agent, coupled to the isotope ^{131}I as the irradiation agent. Neuroblastoma cells often show preferential uptake of mIBG, which is a molecular analogue of a precursor of catecholamines which are commonly made by cells of the sympathetic nervous system. Clinical studies are in progress in the use of ^{131}I-mIBG for targeted radiotherapy of neuroblastoma, and preliminary clinical observations are encouraging. However, dosimetric and radiobiological studies have suggested that a combined radiation modality treatment strategy (^{131}I-mIBG, TBI, bone marrow rescue, local radiotherapy) would be more effective than any one component used alone. Clinical studies have just begin to evaluate this strategy (chapter 3.7). If successful, it would imply that three radiation modalities should be used together in the treatment of suitable cases of neuroblastoma.

this stud
ıroblaston
different
rapy usin
is expect
st use of

AIM OF THE WORK