Hypofractionated and Stereotactic Radiation Therapy

A Practical Guide

Orit Kaidar-Person
Ronald Chen
Editors

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Prof. Kaidar-Person would like to dedicate this book in memory of her mentor, Prof. Abraham Kuten, who was a compassionate doctor, mentor, researcher, and family man. A national and international leader in oncology. He will be thoroughly missed.

Prof. Chen would like to dedicate this book to his wife Petronella Muresan, an incredible mother and outstanding statistician; and to their children, Luke Chen and Matthew Chen.

Preface

Radiation therapy (RT) continues to evolve rapidly as a result of improvements in imaging, advances in patient immobilization and treatment delivery technologies, and our understanding of radiobiology. There are currently two major trends in RT, shortening treatment (hypofractionation) and use of stereotactic radiosurgery and stereotactic body radiotherapy technologies. As published data continue to rapidly accumulate, these treatments are no longer exclusive to specialized centers. Shortening treatment is also appealing to patients because of increased convenience, less interference with planned systemic therapy, and is often less costly than conventionally fractionated (longer) RT courses. Radiation therapy continues to be, and is increasingly so, an effective and cost-effective cancer treatment that reduces cancer-specific mortality (CSM) and overall mortality for many cancers.

This handbook was developed to summarize the data and techniques for hypofractionation and stereotactic radiation in a clinically accessible way, providing concise information ranging from commonly used dose-fractionation schemes to simulation and treatment specifications to published safety and efficacy data. While hypofractionation and stereotactic radiation are used in almost all cancer sites, we note where there are strong supportive data including randomized trials, and other areas where relatively little data are available to guide treatments. Further, we want to highlight that the development of a stereotactic radiotherapy program requires specialized expertise and quality assurance procedures, which are described in Chap. 3.

We hope that you will enjoy the book as much as we enjoyed the process of developing it. This handbook was written to be practical, with usable information relevant for the clinician. We want to thank all the contributors of this book for their hard work and expertise.

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Abbreviations

3D	3-Dimensional
3DCRT	3-Dimensional conformal radiotherapy
4D	4-Dimensional
4DCRT	4-Dimensional conformal radiotherapy
5-FU	5-Fluorouracil
AA	Anaplastic astrocytoma
AAPM	American Association of Physicists in Medicine
Ab	Antibody
ABMT	Autologous bone marrow transplant
ABS	American Brachytherapy Society
abstr.	Abstract
ACOSOG	American College of Surgeon Oncology Group
ACS	American Cancer Society
ACTH	Adrenocorticotropic hormone
ADL	Activity of daily living
ADR	Adverse drug reaction
ADT	Androgen deprivation treatment
AE	Adverse event
AFP	Alpha fetoprotein
AIDS	Acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
ALL	Acute lymphocytic leukemia
ALND	Axillary lymph node dissection
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMD	Dactinomycin
AML	Acute myeloid leukemia
AP	Anterior-posterior
APBI	Accelerated partial breast irradiation
APR	Abdominoperineal resection
ARC	Arc therapy

ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AUC	Area under the curve
AVM	Arteriovenous malformations
b.i.d	Twice a day (bis in die)
Bcc	Basal cell carcinoma
BCG	Bacillus Calmette-Guerin
BCS	Breast-conserving surgery
BCT	Breast-conserving treatment (lumpectomy and radiotherapy)
BED	Biological effective dose
BEV	Beam's eye view
BMJ	*British Medical Journal*
bPFS	Biochemical progression-free survival
BRCP	Borderline resectable pancreatic cancer
BUN	Blood urea nitrogen
Bx	Biopsy
c	Cycles (e.g., for two cycles)
ca	Cancer
CALGB	Cancer and Leukemia Group B
CaSS	Cancer-specific survival
CBC	Complete blood count
CBCT	Cone beam CT
cc	Cubic centimeter
cCR	Clinical complete response
CEA	Carcinoembryonic antigen
CESS	German Cooperative Ewing's Sarcoma Study
cGy	CentiGray
Chemo	Chemotherapy
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Conformity index
CIS	Carcinoma in situ
cm	Centimeter
CN	Cranial nerve (e.g., CN X)
COG	Children's Oncology Group
CR	Complete response
Cr	Creatinine
CRC	Colorectal carcinoma
CRM	Circumferential resection margin
CRT	Chemo-radiotherapy
CSF	Cerebrospinal fluid
CSI	Craniospinal irradiation
CSS	Cause-specific survival
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CT-SIM	CT simulation

CTV_x	Clinical target volume x = 1, 2, 3,…
Cu	Copper
CXR	Chest X-ray
CY	Cyclophosphamide
CyK	CyberKnife
D&C	Dilation and curettage
DCIS	Ductal carcinoma in situ
DES	Diethylstilbestrol
DFS	Disease-free survival
DIBH	Deep inspiration breath hold
dL	Deciliter
DLBCL	Diffuse large B cell lymphoma
DLCO	Diffusing capacity
DM	Distant metastases
Dmax	Maximum dose
DRE	Digital rectal exam
DRR	Digitally reconstructed radiograph
DSS	Disease-specific survival
DVH	Dose-volume histogram
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EBRT	External beam radiation therapy
EBUS	Endobronchial ultrasound
EBV	Epstein–Barr virus
ECE	Extracapsular extension
ECOG	Eastern Cooperative Oncology Group
ED	Erectile dysfunction
EDTA	Ethylendiaminetetraacetic acid
EFRT	Extended field radiotherapy
EFS	Event-free survival
EGD	Esophagogastroduodenoscopy
EGJ	Esophagogastric junction
EIC	Extensive intraductal component
ENT	Ear nose throat
EORTC	European Organisation for Research and Treatment of Cancer
EPID	Electronic portal imaging device
ER	Estrogen receptor
ERBB	Epidermal growth factor
ERCP	Endoscopic retrograde cholangiopancreatography
ESR	Erythrocyte sedimentation rate
ESTRO	European Society for Radiotherapy and Oncology
ESRTO ACROP	ESTRO and the Advisory Committee in Radiation Oncology Practice
ETE	Extra-thyroid extension
EtOH	Alcohol
EUA	Exam under anesthesia

EUS	Endoscopic ultrasound
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
FEV_1	Forced expiratory volume in 1 second
FFF	Freedom from failure
FFP	Freedom from progression
FFS	Failure-free survival
FH	Family history
FIGO	International Federation of Gynecology and Obstetrics staging system
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
FOBT	Fecal occult blood test
FSH	Follicle-stimulating hormone
FSRT	Fractionated stereotactic radiotherapy
FSU	Functional subunit
FWHM	Full width half maximum
fx	Fraction(s)
GaK	GammaKnife
GBM	Glioblastoma multiforme
GEC-ESTRO	Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology
GERD	Gastroesophageal reflux disease
GH	Growth hormone
GHSG	German Hodgkin's Study Group
GIST	Gastrointestinal stromal tumors
GITSG	Gastrointestinal Tumors Study Group
GOG	Gynecologic Oncology Group
GS	Gleason score
GTR	Gross total resection
GTV	Gross tumor volume
GU	Genitourinary
Gy	Gray
H&E	Hematoxylin and eosin
H&N	Head and neck
H&P	History and physical exam
HAART	Highly active retroviral therapy
Hb	Hemoglobin
Hcc	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDR	High dose rate
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HNPCC	Hereditary nonpolyposis colon cancer

HNSqCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HRT	Hormone replacement therapy
HSRT	Hypofractionated stereotactic radiotherapy
HT	Helical tomotherapy
HTN	Hypertension
HVL	Half-value layer
Hx	History
IC	Intracavitary
ICRU	International Commission of Radiation Units and Measurements
ICU	Intensive care unit
IDC	Invasive ductal carcinoma
IDL	Isodose line
IE	Ifosfamide and etoposide (VP-16)
IESS	Intergroup Ewing's Sarcoma Study
IFN	Interferon
IFRT I	Involved-field radiotherapy
IGRT	Image-guided radiotherapy
IJROBP	International Journal of Radiation Oncology Biology Physics
ILC	Invasive lobular carcinoma
IM	Internal margin
im	Intramuscular
IMN	Internal mammary nodes
IMRT	Intensity-modulated radiotherapy
INSS	International Neuroblastoma Staging System
Int	Intergroup
IORT	Intraoperative radiation therapy
IS	Interstitial
is	in situ
ISRT	Involved site radiotherapy
ITV	Internal target volume [ITV = CTV + IM]
iv	Intravenous
IVC	Inferior vena cava
IVP	Intravenous pyelogram
JCO	*Journal of Clinical Oncology*
JPA	Juvenile pilocytic astrocytoma
KPS	Karnofsky Performance Status
LAPC	Locally advanced pancreatic cancer
LAR	Low anterior resection
LC	Local control
LCIS	Lobular carcinoma in situ
LCSG	Lung Cancer Study Group
LDH	Lactate dehydrogenase
LDR	Low dose rate
LET	Linear energy transfer

LF	Local failure
LFFS	Local failure-free survival
LFTs	Liver function tests
LH	Luteinizing hormone
LINAC	Linear accelerator
LN	Lymph node(s)
LND	Lymph node dissection
LR	Local recurrence/relapse
LRC	Local-regional control
LRF	Local-regional failure
LRRFR	Locoregional recurrence-free rate
LVEF	Left ventricular ejection fraction
LVSI/LVI	Lymphovascular space invasion
m	Meter
MALT	Mucosa-associated lymphoid tissue
MESCC	Metastatic epidural spinal cord compression
MFH	Malignant fibrous histiosarcoma
mg	Milligram
MHD	Mean heart dose
MLC	Multileaf collimator
MLD	Mean lung dose
mm	millimeter
mOS	Median overall survival
MRA	Magnetic resonance angiography
MRC	Medical Research Council
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRSI	Magnetic resonance spectroscopy imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximal tolerated dose
MU	Monitor unit
MUGA	Multiple gated acquisition scan
N+	Node positive
N0	Node negative
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCIC	National Cancer Institute of Canada
NED	No evidence of disease
NEJM	*New England Journal of Medicine*
NHL	Non-Hodgkin's lymphoma
NPV	Negative predictive value
NPX	Nasopharynx
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSCLC	Non-small cell lung cancer
NSGCT	Nonseminomatous germ cell tumor

NTCP	Normal tissue complication probability
NWTS	National Wilms' Tumor Study
OAR	Organ at risk
OD	Oligodendroglioma
OPX	Oropharynx
ORN	Osteoradionecrosis
OS	Overall survival
PA	Posterior-anterior
PALN	Para-aortic lymph node
Pb	Lead
pCR	Pathologic complete response
PDR	Pulsed dose rate
PET	Positron emission tomography
PLAP	Placental alkaline phosphatase
PNET	Primitive neuroectodermal tumor
PNI	Perineural invasion
PORT	Postoperative radiotherapy
Post-op	Postoperative
PPV	Positive predictive value
pR	Partial response
PR	Progesterone receptor
Pre-op	Preoperative
PRL	Prolactin
prn	as required
PRV	Planning organ at risk volume [PRV = OAR + IM + SM]
PS	Performance status
PSA	Prostate-specific antigen
PTV_x	Planning target volume $x = 1,2\ldots$
PUVA	Psoralen and ultraviolet light A
q.d	Once daily
q.i.d	Four times a day (quater in die)
q.o.d	Every other day
QA	Quality assurance
QALY	Quality-adjusted life year
QC	Quality control
QOL	Quality of life
RAI	Radioactive iodine
RBE	Relative biological effectiveness
RCC	Renal cell carcinoma
Rct	Randomized controlled trial
RFA	Radiofrequency ablation
RFS	Relapse-free survival
RILD	Radiation-induced liver disease
RP	Radical prostatectomy
RT	Radiotherapy

RTOG	Radiation Therapy Oncology Group
s/p	Status post
SBRT	Stereotactic body radiotherapy
SCID	Severe combined immunodeficiency
SCLC	Small cell lung cancer
SCV	Supraclavicular
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	Sacroiliac
SIADH	Syndrome of inappropriate antidiuretic hormone
SINS	Spinal Instability Neoplastic Score
SLNB	Sentinel lymph node biopsy
SM	Set up margin
SMA	Superior mesenteric artery
SMV	Superior mesenteric vein
SNUC	Sinonasal undifferentiated carcinoma
SOB	Shortness of breath
SPECT	Single-photon emission computed tomography
SPEP	Serum protein electrophoreses
SqCC	Squamous cell carcinoma
SRS	Stereotactic radiosurgery
STAPLE	Simultaneous Truth and Performance Level Estimation
STD	Sexually transmitted disease
STIR	Short Tau Inversion Recover (MRI)
STLI	Subtotal lymphoid irradiation
STR	Subtotal resection
SWOG	Southwest Oncology Group
T&O	Tandem and ovoid
t.i.d	Three times a day (ter in die)
TACE	Transarterial chemoembolization
TAH/BSO	Total abdominal hysterectomy/bilateral salpingo-oophorectomy
TBI	Total body irradiation
TBNA	Transbronchial needle aspiration
TCC	Transitional cell carcinoma
TCP	Tumor control probability
TG101	AAPM Task Force Group 101
TME	Total mesorectal excision
TMP/SMX	Trimethoprim/sulfamethoxazole
TMZ	Temozolomide
TNM	Tumor node metastasis
TPS	Treatment planning system
TRUS	Transrectal ultrasound
TSH	Thyroid-stimulating hormone
TTP	Time to tumor progression

TURBT	Transurethral resection of bladder tumor
UA	Urinalysis
UCSF	University of California, San Francisco
UKCCCR	United Kingdom Coordinating Committee on Cancer Research
UNC	University of North Carolina
UNC-CH	University of North Carolina Chapel Hill
UPEP	Urine protein electrophoreses
US	Ultrasound
USA	United States of America
USO	Unilateral salpingo-oophorectomy
UVB	Ultraviolet light B
VAC	Vincristine, actinomycin-D, and cyclophosphamide
VAIN	Vaginal intra-epithelial neoplasia
VCR	Vincristine
VDC	Vincristine, doxorubicin, cyclophosphamide
VDCA	Vincristine, doxorubicin, cyclophosphamide, and actinomycin-D
VEGF	Vascular endothelial growth factor
VM	Vincristine and melphalan
VMAT	Volumetric arc radiotherapy
VP-16	Etoposide
WART	Whole abdominal radiotherapy
Wbc	White blood cell count
WBI	Whole breast irradiation
WBRT	Whole brain radiotherapy
WHO	World Health Organization
WLE	Wide local excision

Chapter 1
The History and Radiobiology of Hypofractionation

Elaine M. Zeman

1.1 Introduction

The use of hypofractionation in radiation therapy is not a new concept. In fact, it is a very old one, dating back to the first third of the twentieth century, the earliest days of the field that would evolve into today's specialty of radiation oncology. Since its earliest incarnation, however, hypofractionation has been "repurposed" for today's use, thanks to more than a century of advances in physics and imaging that now allow most normal tissue to be excluded from the radiation field, something arguably inconceivable in 1900.

To better understand why hypofractionation was largely abandoned by the late 1920s, only to re-emerge at the beginning of the twenty-first century, an overview of the histories of both radiation therapy and radiation biology is in order. In many ways, these two disciplines evolved in parallel. With a few notable exceptions, for nearly 60 years advances in radiation therapy were empirically based, and advances in radiobiology were seldom of clinical utility. This began to change during the 1950s.

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1.2 Historical Context

1.2.1 The Early History of Fractionation in Radiotherapy

At the turn of the twentieth century, X-rays were discovered by German physicist Wilhelm Röntgen, who described them as invisible, "mysterious" emissions from energized vacuum tubes that were capable of producing fluorescence in platinocyanide salts [1]. The following year, French physicist Henri Becquerel identified similar emanations from natural substances—compounds of the element uranium—that didn't require an external energy source, yet like visible light, could expose photographic film [2]. Another year later, Pierre and Marie Curie identified and isolated some of the elements responsible for this "radioactivity" phenomenon, including radium, thorium, and polonium [3]. That X-rays and radioactive sources (emitting γ-rays) had potential medical applications for both imaging and cancer treatment was immediately obvious, and between 1896 and 1900, the nascent field of radiation therapy, as practiced by dermatologists and surgeons of the day, had already claimed cures of both benign and malignant skin conditions [4–6].

In the earliest days of radiotherapy, both X-ray machines and radium applicators were used for cancer treatment, although the greater availability, convenience, and portability of X-ray tubes afforded them a distinct advantage. Add to this the fact that X-ray machines offered, as the technology improved, much higher intensities of radiation output than low-activity radium sources, radiotherapy using X-rays (termed teletherapy) quickly became the international standard. Nevertheless, the use of radioactive sources continued to be developed and refined by the French, a practice that evolved into modern day brachytherapy.

Lacking an understanding at the time of the physical nature of ionizing radiation and how to quantify radiation dose, let alone an understanding of its biological effects, various "philosophies" developed as how best to treat patients. One fundamental radiotherapy principle was recognized early on: the concept of the therapeutic ratio, a risk-versus-benefit approach applied to treatment planning (Fig. 1.1).

In theory, any malignancy could be eradicated simply by delivering a sufficiently high radiation dose. However, in practice, injury to normal tissues that were necessarily irradiated along with the tumor limited the total dose that could be administered safely. Therefore, a balance had to be struck between what was considered an acceptable probability of radiation-induced damage to normal tissue, and the probability of tumor destruction.

Because surgeons were among the early practitioners of radiation therapy, from about 1900 into the 1920s, a prevailing strategy was to view radiotherapy as akin to surgery; that is, to attempt to eradicate the tumor in a single procedure using a large, "tumoricidal" dose. This massive dose technique [7, 8] became a common way of administering radiation therapy, and a (somewhat arbitrary) biological interpretation was also provided: tumors would become increasingly resistant to radiotherapy if too many doses were given, and normal tissues would be preferentially damaged due to "cumulative injury," so it would be preferable to deliver the radiation therapy

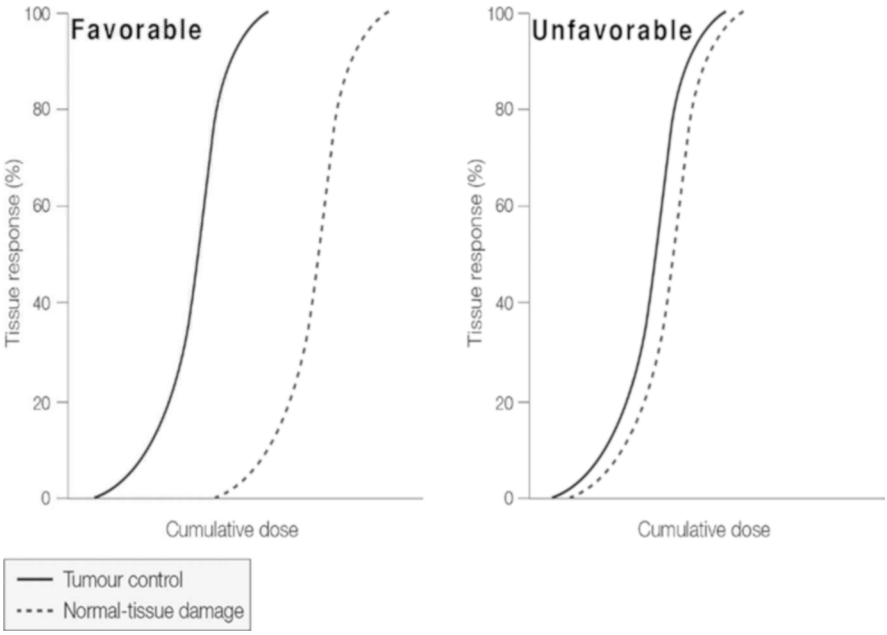

Fig. 1.1 The therapeutic ratio concept, depicted graphically. A favorable therapeutic ratio implies that the radiation response of the tumor is greater than that of the surrounding normal tissue (left panel). In the case of an unfavorable therapeutic ratio (right panel), there is no possibility of obtaining good tumor control without significantly damaging the normal tissue(s) at risk. (Adapted from Bernier et al. [7])

as one or a few large doses over no more than a few days [9]. However, it soon became obvious that this approach did not optimize the therapeutic ratio and that the biological rationale was incorrect; normal tissue complications were typically quite severe, and to make matters worse, the rate of local tumor recurrence was unacceptably high. An early example, in this case involving treatment of a benign hairy nevus, is shown in Fig. 1.2.

As mentioned previously, radium therapy was used more extensively in France. Radium applications involved longer overall treatment times in order to reach total doses comparable to those achieved with X-rays because of the low activity sources. Although multi-day treatments were less convenient in terms of patient throughput, clinical outcomes were often superior for skin and cervix cancers than for X-ray therapy. Brachytherapy proponents also offered a biological rationale, one that was better based on laboratory research than on theory or conjecture. As early as 1906, two French radiation biologists, Bergonié and Tribondeau, observed histologically that undifferentiated, rapidly dividing spermatogonia of the rat testis showed evidence of damage at lower radiation doses than well-differentiated, non-dividing cells of the testicular stroma. Based on these observations, they put forth some basic "laws" stating that radiotherapy was selective for cells that were (1) actively dividing; (2) capable of dividing for extended periods; and (3) poorly or undifferentiated

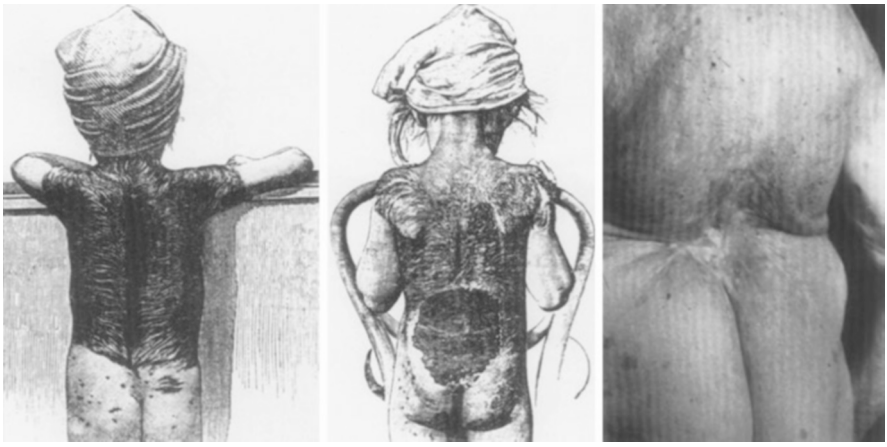

Fig. 1.2 Time course for radiation effects in the skin of a child treated during the "massive dose" era for an extensive hairy nevus before treatment (left), a week after the end of treatment (middle) and 75 years later (right). Acutely, the skin injury consisted of a large area of confluent moist desquamation, but over time, fibrosis, necrosis, and poor wound healing was observed and persisted over the patient's lifetime. Few patients were cured using this large dose, large volume technique, and typically died long before normal tissue damage became manifest. In this particular case, however, the (benign) hairy nevus was eradicated. (Adapted from Kogelnik [5])

[10]. Some tumors were already known at that time to contain cells that were less differentiated and more proliferative than most normal tissues. Accordingly, Bergonié and Tribondeau reasoned that multiple radiation exposures would preferentially kill these tumor cells, while preserving their slowly proliferating, differentiated counterparts in the normal tissues included in the radiation field.

During the 1920s, the massive dose technique began to fall out of favor, particularly in light of the pioneering experiments of Claude Regaud and colleagues, who built on Bergonié and Tribondeau's earlier work [11]. Regaud cleverly used the testes of the rabbit as a model system, reasoning that the process of sperm production (i.e., relatively undifferentiated cells proliferating rapidly and indefinitely) mimicked to a first approximation the behavior of tumors, and that the scrotum could be used as a representative dose-limiting normal tissue. Regaud showed that only through the use of multiple, smaller radiation doses could animals be completely sterilized without producing severe injury to the scrotum [12].

These principles were soon tested in the clinic by French physician Henri Coutard, who used multiple small x-ray doses delivered over extended periods in human patients [13]. Clinical outcomes for patients with head and neck cancer were improved to such an extent that fractionated radiation therapy using many small dose increments spread over several weeks' time soon became the standard of care [13, 14], and has largely remained so to the present day.

Summary: relevance to today's use of hypofractionation

- During the early days of radiotherapy—the first 30 years of the twentieth century—extreme hypofractionation using one or a few very large doses was a treatment standard.
- It was subsequently abandoned when it became clear that tumor control was poor and normal tissue complications severe.
- Early research in radiation biology determined that the best way to optimize the therapeutic ratio was to deliver many small dose fractions over a period of weeks.
- Translating this information into the clinic, fractionated radiotherapy using small doses delivered over several weeks provided much improved outcomes, and became the new standard of care.

1.2.2 Isoeffect Relationships

Once fractionated radiotherapy became the new standard of care a different problem emerged, namely how different practitioners with somewhat different approaches to fractionation, e.g., how many fractions delivered, time between fractions, total dose, overall treatment time, etc., could be inter-compared in terms of tumor control and normal tissue complication probabilities. One approach was to determine "equivalents," that is, treatment combinations that yielded similar outcomes. Time-dose equivalents for skin erythema were published by several investigators [15–18] and these formed the basis for the calculation of equivalents for other normal tissue and tumor responses. By plotting the total dose required for a particular equivalent in a particular tissue, as a function of one of the variable treatment parameters (overall treatment time, number of fractions or dose per fraction), a so-called isoeffect curve could be derived. All time and dose combinations that comprised an isoeffect curve for a certain endpoint would, theoretically, produce tissue or tumor responses of equal magnitude.

Also better appreciated during the 1930s was how and when normal tissue complications occurred after treatment, and their severity as a function of total dose. Presumably, these complications were the result (directly or indirectly) of the killing of critical cells within the tissue, so the higher the radiation dose, the more cells were killed and the more severe the complication. It was also clear that skin, the dose-limiting normal tissue in most cases, could manifest more than one complication and that each seemed to have its own threshold or tolerance dose before the complication occurred, a reflection of the tissue's radiosensitivity. However, the "earliness" or "lateness" of the clinical manifestation of that injury was a separate phenomenon more related to the cellular renewal pattern of the tissue.

The first published isoeffect curves were produced by Strandqvist in 1944 [19], and shown in Fig. 1.3. When plotted on a log–log scale of total dose versus overall treatment time, isoeffect curves for a variety of skin reactions, and the cure of skin cancer, were drawn as parallel lines.

As drawn, Stranqvist's isoeffect curves suggested that there would be *no* therapeutic advantage to using prolonged treatment times and multiple small dose

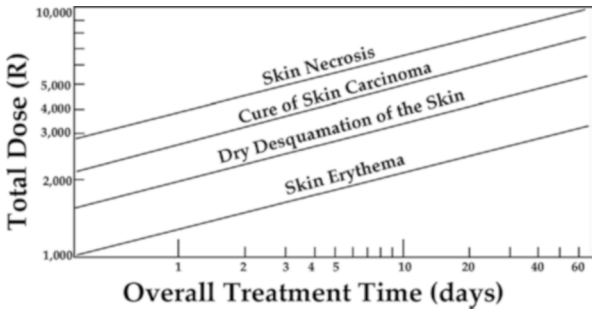

Fig. 1.3 Strandqvist's isoeffect curves, first published in 1944, plotted the log of the total dose to achieve the measured isoeffect as a function of the overall treatment time. The shorter the overall treatment time, the more hypofractionated the schedule, and the lower the dose required to produce the isoeffect. (Modified from Strandqvist [19])

fractions for the preferential eradication of tumors while staying within the tolerance of the normal tissue [20]. Ironically however, it was already known that the therapeutic ratio *did* increase with prolonged, as opposed to very short, overall treatment times. Nevertheless, the reliability of these curves at predicting skin reactions, which were the dose limiting at the time, made them quite popular.

Nearly 25 years after Strandqvist, Ellis [21, 22] revisited his popular isoeffect curves, and armed with new knowledge about the radiobiology underlying fractionation effects in pig skin [23, 24], formulated the NSD concept in 1969. The NSD equation,

$$\boldsymbol{D = (\mathrm{NSD})\, N^{0.24} T^{0.11}},$$

where D is the total dose delivered, N the number of fractions used, T the overall treatment time, and NSD the nominal standard dose (a proportionality constant related to the tissue's tolerance), became widely used, particularly once mathematically simplified derivatives, such as the TDF equation [25] became available. The major innovation of the NSD model was that the influence of the fraction number had been separated from the influence of the overall treatment time, and in fact, the fraction number (and therefore, size) was the more important of the two.

The introduction of the NSD equation allowed radiotherapy treatment practices world-wide to be compared with respect to putative "biological equivalence," provided it was not used for treatments involving extremes of fraction number or overall time outside the range of the data upon which the model was based (i.e., Strandqvist's curves). It also provided a means of revising treatment prescriptions in the event of unforeseen treatment interruptions. However, the NSD formula was ill-equipped to deal with some clinical issues, in particular the prediction of late effects in normal tissues, which, with the advent of megavoltage linear accelerators capable of treating deep-seated tumors, replaced skin as being dose-limiting [26]. In light of the emerging limitations of the NSD model, there was a need for new, radiobiologically based approaches to isoeffect modeling.

Summary: relevance to today's use of hypofractionation

- Isoeffect curves plot the total dose required for a particular tumor or normal tissue endpoint as a function of one of the variable treatment parameters, such as overall treatment time or number of fractions. All time-dose combinations that fell on a particular isoeffect curve were considered biologically equivalent.
- Isoeffects of interest included tumor control and various normal tissue complications, typically in skin, such as desquamation, necrosis, or fibrosis.
- Some complications occurred during or soon after the completion of radiotherapy, "early effects," and others took months or years to manifest, "late effects."
- The total dose required to cause a particular complication was a reflection of the tissue's radiosensitivity, but the time it took for the complication to appear was related to the tissue's natural cell renewal process.
- A mathematical model derived from isoeffect curves, the NSD equation, allowed the calculation of biological equivalents for different treatment schedules. Yet because the model was based on early skin reactions, it was poorly equipped to model late complications in normal tissues. With the advent of megavoltage radiotherapy equipment that allowed treatment of deep-seated tumors, damage to internal organs rather than skin became dose-limiting, and many of these expressed their injuries as late effects.

1.2.3 Tumor Hypoxia

As early as 1909, it was recognized that decreasing blood flow during radiotherapy leads to a reduction in the prevalence or severity of radiation-induced skin reactions [7, 8], although at the time, the mechanism for this effect was unclear. Decades later, chemists and biologists determined that the presence or absence of oxygen was the key, and that the mechanism of oxygen's action was to interact with free radicals produced during irradiation, thereby enhancing the damage to cellular macromolecules. In other words, oxygen acted as a radiation sensitizer. Thus, the relative *absence* of oxygen in an irradiated system meant less molecular damage, and therefore, greater radioresistance.

In 1955, however, Thomlinson and Gray [27] brought this idea to the forefront of radiation biology and radiation therapy by proposing that tumors contained a fraction of oxygen-starved yet still reproductively viable (i.e., "clonogenic") hypoxic cells and that if these persisted throughout the course of fractionated radiotherapy, they would adversely affect the therapeutic ratio. The oxygen enhancement ratio (OER) is a metric developed to quantify how much more radioresistant hypoxic cells were than well-aerated ones. For large, single radiation doses, OER values of 2.5–3.0 were typical, but for conventional radiotherapy using repeated, small dose fractions delivered over several weeks, the OER was lower, typically in the range of 1.5–2.0 [28].

Accordingly, if human tumors contained even a tiny fraction of clonogenic hypoxic cells, simple calculations suggested that tumor control would be nearly impossible [29], even for high doses. The total dose needed to control such tumors would become prohibitive because normal tissues are not hypoxic and therefore would experience higher complication rates if the total dose were increased. In fact, the only way that hypoxic tumor cells would *not* constitute a treatment impediment was if extended periods of hypoxia eventually led to their deaths, that these cells "reoxygenated" during the course of treatment and/or that they were not clonogenic to begin with.

Hypoxia is a consequence of the abnormal vasculature characteristic of tumors. Such blood vessels are the product of abnormal angiogenesis and often are structurally, functionally, physiologically, and/or spatially aberrant which, when combined with the tumor's high oxygen demand and tendency to outgrow its own blood supply, leads to both micro- and macro-regions of hypoxia.

Summary: relevance to today's use of hypofractionation

- Molecular oxygen interacts with free radicals produced during irradiation, enhancing cellular damage. Hypoxic cells that are low in oxygen, but not so low as to result in lethality, can be up to three times more radioresistant than well-aerated ones.
- Vascular abnormalities characteristic of tumors lead to both micro- and macro-regions of hypoxia. Hypoxia is largely absent in normal tissues.
- Simple calculations suggest that tumor control would be impossible—even for the high doses used today in extreme hypofractionation—if human tumors contained even a tiny fraction of clonogenic hypoxic cells, provided they persisted throughout the course of radiotherapy.

1.2.4 The Four R's of Radiotherapy

What was largely lacking during radiotherapy's first half-century was a biological basis for why dose fractionation spared normal tissue complications, and without this information, it was very difficult to determine which biological characteristics of normal or tumor tissues might be exploited to improve the therapeutic ratio. This began to change with the publication in 1975 of a seminal paper entitled "*The Four R's of Radiotherapy*" [30]. The paper was an attempt to explain the biological basis of fractionation by describing in simple terms key radiobiological phenomena thought to affect radiotherapy outcome: *R*epair, *R*epopulation, *R*eoxygenation, and *R*edistribution. In the ensuing years, a fifth "R" was added, *R*adiosensitivity [31], although in some respects, it is inextricably linked to repair. (Redistribution is difficult to measure, yet is assumed to occur in vivo during conventional fractionation. However, it is thought to play only a minor role in treatment outcome and likely has even less of a role for hypofractionation, so will not be discussed further.)

1.2.4.1 Repair and Radiosensitivity

The surviving fraction of cells following a moderate-to-high radiation dose is higher if that dose is split into two increments separated by a time interval than delivered as a single dose, suggesting that cells surviving the initial dose had repaired some of the damage during the radiation-free interval [32]. As such, this damage was no longer available to interact with the damage inflicted by the second dose, so a higher cell surviving fraction resulted. This phenomenon is termed sublethal damage recovery (SLDR). These "split-dose" experiments turned out to be crucial to the understanding of why and how fractionated radiation therapy works, that is, that SLDR was responsible for the greater radiation tolerance of tissues when a large total dose was divided into small dose fractions and protracted over time.

However, this sparing effect of dose fractionation does not continue indefinitely as smaller and smaller (and more numerous) doses are delivered. Instead, a limit is reached where further lowering of the dose per fraction does not produce a further decrease in toxicity. This finding is consistent with the idea that survival and dose response curves have negative initial slopes [33, 34], and that after many, sufficiently small dose fractions are delivered, a "trace" of this initial slope would be obtained.

One important clinical implication of repair and radiosensitivity phenomena is that small differences in shoulder regions of dose response curves for different dose-limiting normal tissues and tumors could be magnified into large differences when many small dose fractions are used compared to a single or a few large fractions. A tissue's radiosensitivity and repair capacity are critically important to the selection of the total dose, dose per fraction and interfraction interval used for radiation therapy, as they govern both the tumor control and normal tissue complication probabilities.

1.2.4.2 Repopulation

Repopulation is defined as an increase in cell proliferation in tissues in response to an injury that produces cell killing. Normal tissues and tumors containing stem or stem-like cells can begin to proliferate during and after a course of radiation therapy, with the timing of this response a function of the proliferation kinetics of the tissue [35, 36], typically during or within 3 months of treatment for "early-responding" normal tissues and most tumors, and more than 6–9 months (if at all) for "late-responding" tissues.

Repopulation is desirable in normal tissues because it facilitates the healing of common radiotherapy complications that develop during or soon after treatment, such as oral mucositis, for example. On the other hand, repopulation of tumor cells is undesirable because it would have the net effect of counteracting ongoing radiation therapy, which in turn would lead to the appearance of tumor "radioresistance" and accordingly, the attendant risk of recurrence. For tumors capable of rapid repopulation that begins during conventional radiotherapy, estimates are that as much as