Oral Cancer

Oral Cancer:

From Prevention to Intervention

By

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CONTENTS

Part Three – Studies

Part Four – Solutions

LIST OF ILLUSTRATIONS

LIST OF TABLES

PREFACE

It is often said that, 'prevention is better than cure'. Whilst the origins of this popular proverb remain obscure, it is an undeniable and simple truism based upon common sense and ultimately life experience. In essence, prevention literally means stopping something happening and it is clearly far better to stop 'something bad' from happening than having to deal with the resultant consequences. Perhaps there is no better example of 'something bad' happening to someone than development of a life threatening disease such as cancer in which prevention can be effective and relatively economical, whilst cure may not only be elusive but also expensive in terms of financial and emotional costs. Cancer is the term colloquially applied to all malignant disease, although strictly speaking actually refers to those invasive and metastasizing tumours that arise from disturbed cell growth and replication within the ubiquitous epithelial lining tissues of the body.

Oral cancer, principally squamous cell carcinoma (SCC), thus arises from the specialized stratified squamous epithelium that, together with its underlying lamina propria of fibro-vascular connective tissue, forms the functional lining mucosa of the mouth, which is of course a significant entry-point into the upper aero-digestive tract and thereby the body itself. Often, though not exclusively, the consequence of over-use of tobacco and alcohol, resultant tumours present as non-healing erosive or ulcerative lesions that subsequently progress to invasive and ultimately painful growths. Established oral cancer is one of the commonest head and neck malignancies, and is a lethal and deforming disease due to local tissue invasion, oral and facial destruction, metastasis to cervical lymph nodes and widespread blood-borne dissemination to the lungs and the liver. Worldwide, it is estimated to be the 6th most common cancer with 5-year survival rates of only 50%, much worse than other more common and better known cancers such as breast or colon. Indeed, annual mortality rates are predicted to rise from around 370,000 to over 600,000 by 2030, raising the genuine spectre of a global epidemic. Individual patient prognosis is compromised by late presentation of advanced and aggressive disease which is sadly all too common in contemporary clinical practice and even initially successful treatment, often a combination of extensive surgical resection and debilitating chemo-radiotherapy, may be

complicated by recurrence or new, multi-focal disease extending throughout the upper aero-digestive tract as a result of widespread epithelial changes; a phenomenon described as ‘field cancerization’.

Immediately prior to invasive SCC development, however, earlier epithelial disorganisation and dysmaturation changes can be identified microscopically and delineated by pathologists into increasingly severe grades of ‘epithelial dysplasia’, thus representing an increased risk of cancer development. Importantly, such changes may be clinically recognizable during conventional oral examination and characterized as mucosal abnormalities, most commonly leukoplakia (a mucosal white patch), and termed potentially malignant disorders (PMD). Whilst all PMD share an increased risk of cancer development compared to ‘apparently normal’ mucosa, not all will inevitably transform, thus creating a challenging management dilemma for clinicians and patients alike.

Is there, therefore, an opportunity for prevention, early diagnosis and low-morbidity therapeutic intervention during this clinically identifiable ‘oral pre-cancer window’ that might ‘stop the oral cancer clock’ and help reduce the long-term risk of malignant transformation? This is an essential question, and forms the fundamental theme of the book you are about to read.

It is important to stress at this juncture that I have not attempted a systematic review of the global oral cancer literature, nor have I undertaken a meta-analysis of treatment intervention. Although of undoubted scientific validity and interest, such a work would be difficult to read and would not serve the particular purpose of this book, which is to guide the reader through a more personalised journey documenting a clinically orientated research programme undertaken by the author, in an attempt to improve both knowledge and understanding of the natural history of oral cancer. Nonetheless, detailed references will be provided in each chapter for those wishing to pursue their studies further.

Perhaps to explain this approach more fully, I should refer the interested reader to the preface of a previously published work on oral pre-cancer, in which I first detailed an approach to the diagnosis and management of PMD and described the genesis of my interest in studying this most intriguing and beguiling of disorders[1]. Nearly 40 years has passed since, as an undergraduate dental student, I first attended specialist oral surgery and oral medicine clinics at a well-known dental teaching hospital in North-West England. It was here that I was introduced to the fascinating and

confusing array of oral mucosal lesions deemed to be PMD and discovered their varied aetiologies, histopathological and clinical diagnoses and, perhaps most significantly of all, their devastating potential to transform to life-threatening cancers.

My early interest and enthusiasm was tempered, unfortunately, by the gradual realisation that my clinical teachers, many of whom were senior clinicians and professors of international repute, were unable to determine the individual risk of patients undergoing carcinogenesis. Nor could they offer reliable prognoses for disease progression or, apparently, any appropriate treatment intervention. Worst of all was to encounter those unfortunate individuals who, despite regular clinic attendance for examination and reassurance, subsequently went on to develop oral cancer.

As I commenced my clinical training in hospital dentistry and then medical undergraduate studies, followed by a period of scientific research in epithelial biology, before specialising as an oral and maxillofacial surgeon I learned a great deal more about the devastating consequences, both in terms of morbidity and mortality, of oral cavity cancer. The personal inspiration to try to combat this pernicious oral disease was born. Could rationalizing oral diagnostic technique and developing an efficacious interventional management protocol improve treatment outcomes for patients? The reader, I hope, will have the opportunity to judge.

Like most clinicians, I owe enormous personal debt to my clinical teachers and surgical trainers through the years, but I particularly wish to acknowledge and thank my patients for their stoicism and loyalty and especially the trust they have bestowed on me as their advisor and surgeon. It is for them, and future patients like them, that this book is dedicated.

Peter Thomson
Hong Kong
2018

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PART ONE

PROBLEMS

'a situation regarded as harmful and needing to be dealt with…'

CHAPTER ONE

A PERSONAL JOURNEY

'…the act of travelling from one place to another…over a long period…'

I do hope that the reader will, at the outset, indulge me with some brief reflection on my personal academic and professional journey. As already alluded to in the Preface, I trust that this will help to place much of what is to follow in perspective and clarify the precise development of many of the hypotheses, theoretical arguments and treatment philosophies described in the subsequent chapters of this book.

Even today, as I rapidly approach my 60th year, I remain unable to explain exactly why, from an early age, I always wanted to be a dentist. Strange in many ways because, like many people growing up in the 1960's, I did not particularly look forward to attending as a dental patient or undergoing treatment at my local practice, despite the consummate skill and consideration I always received. Perhaps it was, indeed, the evident professionalism of my own dentist that catalysed my personal interest and enthusiasm for considering dentistry as a career. To be able to offer specialist knowledge and advice, and provide skilled practical help to people in need was I think what attracted me most about practising as a dentist; it still does to this day.

In 1978, therefore, I was pleased to commence undergraduate studies in the Turner Dental School at the Victoria University of Manchester. Lasting four years and one term in those days, the course was demanding, time consuming and highly rewarding all in equal measures. Gaining both knowledge and practical operative skills, I qualified BDS (Honours) in December 1982 and became a registered practitioner with the General Dental Council; Figure 1.1. During my studies, I particularly enjoyed pathology and medical and surgical subjects, although I never held any particular aspiration to work as a medical practitioner. In my senior student years, as discussed in the Preface, I developed an especial interest in the study of oral cancer and potentially malignant disorders (PMD) and realised that the specialty of oral surgery, particularly in an academic

environment, combined the subjects that interested me most in a particularly challenging and proactive manner. Somewhat ironically for me, 1982 was also the year that oral surgery formally transformed into oral & maxillofacial surgery in the UK, thereby undertaking a broader range of head and neck surgery and appropriately now requiring both dental and medical qualifications for specialist training.

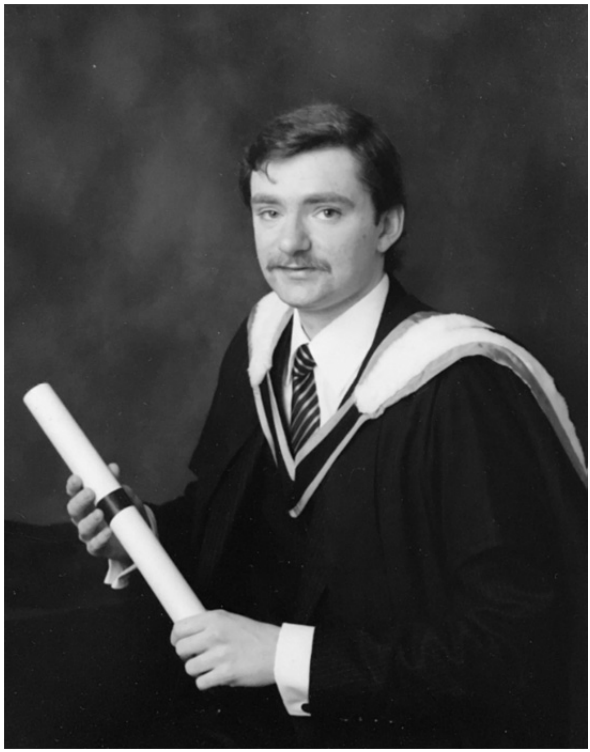

Figure 1.1: The author, graduating BDS from Manchester University, December 1982.

The die was therefore well and truly cast for me. Whilst undertaking my first job as a dentist working as a dental hospital house officer at Manchester in 1983, I applied and was accepted to study medicine at the University of Newcastle upon Tyne, ultimately qualifying MBBS and becoming a medical practitioner in 1988. To be candid, I found medical studies as an undergraduate far less demanding than dentistry, the latter of course requiring significant clinical and practical skill acquisition in

addition to knowledge retention, and I was fortunate to have time, primarily during evenings, weekends and university holidays, to practise part-time as a general dental practitioner in a busy and well-regarded practice within a small mining town in County Durham. Looking back at those happy and fulfilling years, it is impossible to over-emphasize how much experience I truly gained and how much I learned about clinical dental practice; quite simply, invaluable 'real-world' experience for the would-be specialist.

In 1989, after pre-registration medical jobs in Newcastle, I was offered a post as a junior lecturer in oral & maxillofacial surgery back at my alma mater in Manchester. This was the start of my clinical academic career and an exciting time, as I joined a successful and expanding academic surgical department. During this time, I sat the required training examinations gaining Fellowships in Dental Surgery from the Royal College of Surgeons of England and Ireland in 1990 and, following a period of general surgical training, a Fellowship in Surgery from the Edinburgh College in 1992. I was enrolled as a higher trainee and was fortunate to work with a number of outstanding and skilled oral & maxillofacial surgeons; as time went on, it was clear that oral cancer and head & neck oncology was becoming the focus of my clinical training.

A senior colleague in the department at the time, and one far more gifted than I, introduced me to research opportunities at the Paterson Institute for Cancer Research at the Christie Hospital in Manchester. Here I discovered the fascinating science of epithelial cell kinetics and was welcomed as a novice to laboratory research by renowned cell biologists. How they ever tolerated my disruptive, part-time forays into oral carcinogenesis research I will never know, but these astonishingly generous scientists supported and guided me to complete both MSc[1] and PhD[2] research degrees in epithelial biology; I owe them an enormous debt, hence their appearance and recognition, albeit far too briefly, in this book!

In 1996 I had completed my surgical specialty training and, quite unexpectedly and without forewarning, was invited to apply for the newly re-established Chair in Oral & Maxillofacial Surgery in the School of Dentistry at Newcastle University. Although I was only 36 years old, and it genuinely felt premature, I was nonetheless interviewed and appointed to the post. With the prescribed remit of re-invigorating the academic department and developing oral cancer research and teaching, I returned to Newcastle in August of that year as Professor of Oral & Maxillofacial Surgery.

High rates of oral cancer have always existed in Northern England, unfortunately, with the general health of some 280,000 people living in the city of Newcastle upon Tyne worse than average for many parameters documented in England, including reduced life expectancy, high levels of adult smoking and smoking-related deaths, and significant rates of alcohol-related disease and hospital admission. Whilst an average of 70 new cases of oral cancer occurred each year in the region[3], no data existed at all to document the incidence or prevalence of PMD. In an attempt to improve both knowledge and patient management, I established a dedicated PMD clinical service based within the Newcastle Dental Hospital and the Maxillofacial Unit at the Royal Victoria Infirmary. From rather inauspicious beginnings, we were ultimately managing around 1200 patient attendances each year comprising new patient referrals of suspicious oral lesions, forwarded from both primary care practitioners and specialist hospital colleagues, together with the longer-term follow-up of previously diagnosed and treated cases.

A specific interventional management protocol was developed for these patients, based firmly upon those early dental student observations, concentrating upon the recognition of patients with PMD, the early diagnosis and characterization of disease, the removal or ablation of 'high risk' 'pre-cancer' mucosal lesions by CO_2 laser (a technique I was first introduced to in Manchester) and structured patient follow-up and surveillance[4]; much of this will be examined and discussed in detail later in the book.

Looking back, the ensuing 20 years literally flew by as my colleagues and I worked hard to build effective clinical, teaching and research capabilities for our specialty of oral & maxillofacial surgery. It was hard work, not always without professional opposition to our desire to grow and develop, but steady progress continued, students were taught, research papers published and patients increasingly treated to the highest standards we could achieve.

In 1999, following a merger of adjacent NHS hospital trusts, a particularly important and welcome development was the formation of the Northern Head & Neck Cancer Unit. Based at Newcastle's Freeman Hospital, a functioning and truly innovative, multi-disciplinary head & neck cancer service was developed and delivered for the first time with surgeons from different specialities combining their expertise, and with oncologists and patient supportive services fully coordinated to centralise and prioritise exemplary patient care. This, of course, has now become the model for

cancer centres throughout the UK and indeed globally to improve diagnosis and management for patients; but Newcastle was one of the first!

Working 'hand in glove' with colleagues, we continued to integrate services for patients to build the best specialist oncology centre we could in Newcastle. Research in our discipline continued to prosper too; with an increase in academic and clinical staff came more publications, new postgraduate students and an expanding profile of research income. My own work continued in a concerted attempt to improve the overall efficacy of diagnosis and management for PMD and, in particular, the early identification and treatment of oral SCC.

In 2002, we had the opportunity to join a major, Europe-wide epidemiological study to stratify risk assessment for oral cancer development, especially in relation to lifestyle habits, dietary factors and occupation. Following appropriate ethics committee approval, we recruited 73 Newcastle oral cancer patients and 112 controls into the Alcohol Related Cancers and Genetic susceptibility in Europe (ARCAGE) study. Ultimately, this project examined data of 2304 head and neck cancer cases and 2227 controls from 15 centres in 11 European countries, adding significantly to our understanding of the epidemiology and aetiology of oral cancer[5]. After some years of continuing and productive research, we then became part of the even larger International Head and Neck Cancer Epidemiology (INHANCE) consortium, which together collated data from 14,520 head and neck cancer cases and 22,737 controls[6]. These were indeed exciting times, with 'big data' sets to analyse, providing outstanding opportunities to advance our knowledge of oral carcinogenesis; many of the resulting publications from these research collaborations are referenced throughout this book. I am delighted to report that this work is still on-going as I write!

In 2009, I was honoured to be appointed Hunterian Professor at the Royal College of Surgeons of England, followed in 2011 by a King James IV Professorship at the Royal College of Surgeons in Edinburgh in recognition of my research and clinical work in oral oncology and the advancement of surgical care, respectively. In 2012, I edited and published my book on PMD management, which I hope the reader will find a suitable and complementary companion volume to this work[7], and in 2014 gained a higher doctorate (DDSc) from Manchester University for my collected published works on oral cancer research[8]. This was followed in 2016 by an MD thesis from the University of Bath detailing the results of

interventional management of PMD over a 20-year period[9]; we will carefully examine these substantive data in a later chapter.

In 2014, after a very rewarding but personally exhausting 4-year stint as Clinical Director of the Dental Hospital, I took sabbatical leave from Newcastle and spent a term as Visiting Professor at the National University of Singapore, which enjoyably and quite spectacularly expanded my global view of dental education, training and research. Shortly afterwards, I was invited to consider becoming the new Head of School at a dental teaching institute in Australia. Although extremely tempting, both the local university and I ultimately decided that this was not the right time or place for me; looking back now, I realise that was probably a wise decision.

The Asia-Pacific experience did, however, significantly alter my outlook on my professional life to date and, after nearly 20 years in Newcastle, I realised it was time to seriously consider some change and professional renewal. I had, after all, developed, staffed and led a modern and innovative clinical academic department, mentored young colleagues to develop their clinical, research and managerial skills, and worked hard to ensure full integration of clinical services with teaching and research. I really felt that, in order to develop my own skills further, I needed a new professional challenge.

In April 2016, therefore, when an opportunity arose I took a leap of faith and joined the University of Queensland's School of Dentistry in Brisbane as Professor of Oral & Maxillofacial Surgery and Academic Clinical Director; an exciting move tinged, of course, with some sadness as I left many colleagues, friends and patients behind in the UK. The newly commissioned Oral Health Centre, located at the University's Herston campus, possessed the most modern dental facilities I have ever seen and it was an absolute pleasure to teach and practice there. Within a year, I was asked to take on the new role of Oral Health Alliance Director to lead the conjoint delivery of oral health services and teaching between the University of Queensland and Metro North Hospitals and Health Service, the local provider of public health services[10]. This became a fascinating project as we essentially deconstructed the existing University-led clinical service to reconfigure a new public oral health service; I wonder how similar it must have been during the launch of the NHS in the UK some 70 years beforehand!

And finally…to the present day when, after a receiving an enticing offer but facing a very difficult decision making period, I left Brisbane in September 2017 having accepted the post of Clinical Professor and Head of Oral & Maxillofacial Surgery at the University of Hong Kong's Faculty of Dentistry[11]. At the time of writing the World's number one ranked dental school for three consecutive years, I hope that the extraordinary vibrant academic environment here and personal interaction with outstanding colleagues will help me to refine and consolidate my on-going research work in oral oncology; we begin again![12].

Quite a journey then from the Turner Dental School in Manchester 40 years ago, especially when summarised, edited and fast-tracked over 4 pages or so of text, but in reality just the background scene setting for the detailed story about to unfold.

Figure 1.2: Hong Kong, March 2018

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CHAPTER TWO

ORAL CANCER

'…know your enemy…'

Introduction

Perhaps somewhat ironically, in view of the title, this is not actually a book about oral cancer. On the contrary, it is very much a manuscript dedicated to the prevention of cancer by the early diagnosis of pre-cancerous or pre-malignant change and the development of effective, minimally invasive interventional strategies to halt the progress of oral carcinogenesis. Nonetheless, if we are to be truly successful in our battles with this pernicious and lethal disease I think it is very important at this juncture that we take time to try to understand more fully the true nature of our enemy.

What is Cancer?

It is estimated that one in three people will develop cancer at some point in their life; quite a sobering statistic. To address the titular question, cancer is essentially a genetic disorder resulting from accumulation of multiple mutations in cellular DNA, particularly those resulting in cell immortality and the loss of response to normal growth control mechanisms. Originally termed 'cancer' due to the microscopically observed 'crab-like' projections of abnormal epithelium invading subjacent connective tissue, malignant tumour formation involves a complex, multi-stage disruption to the processes of cell proliferation, differentiation and development[1].

An established tumour is thus an abnormal, uncoordinated tissue growth that persists in an excessive manner after the initiating stimuli have ceased. Tumour initiation and then progression may result from damage caused by extraneous physical, chemical or biological agents which are termed carcinogens, or unpredictably by spontaneous mutation. Uncontrolled growth facilitates local tissue invasion and destruction, including direct

involvement of adjacent nerves, blood vessels and lymphatics. Loss of cell adhesion leads to metastasis and widespread organ involvement by tumour seeding. A battle for nutritional resource, and ultimately biological survival, ensues between tumour and host. In the absence of effective treatment intervention, the host becomes progressively weakened by the ever increasing tumour mass, giving rise to classical clinical signs of malignancy including cachexia, anaemia and muscle wasting, before progressing to organ failure and death.

In recent years, somatic stem cells, the adult tissue equivalent of their embryonic counterparts, have been postulated as the primary target cell in carcinogenesis. Such activated 'cancer stem cells' may be responsible not only for tumour growth, but also for the development of metastases, treatment resistance and ultimately recurrent disease[2].

Whilst tumours arising from accessible epithelial surfaces such as skin and oral mucosa may be readily observed upon clinical examination, others arising in deeper body structures may require endoscopic examination or advanced imaging with techniques such as CT or MR scanning. Once identified, biopsy and histopathological grading is essential for the diagnostic process[3].

Cancer treatment involves one or quite often a combination of the following aggressive treatment modalities: surgery, radiotherapy and chemotherapy. These are increasingly combined in specific regimes, devised and prescribed in multi-disciplinary specialist cancer clinics, in an attempt to improve efficacy. Conventional surgery requires access techniques at operation to facilitate full tumour visualisation and resection with a margin of adjacent normal tissue in anticipation of local invasion, and excision of draining lymph nodes to address metastatic spread. The application of ionising radiation as localised radiotherapy to the primary tumour site is performed to preferentially destroy rapidly proliferating tumour tissue, albeit at the expense of damaging normal tissue, or following surgery to 'sterilise' the operative field of residual tumour cells. Chemotherapy offers similar effect, targeting actively dividing cells to eliminate tumours whilst allowing normal cells to repair, but is administered as systemic treatment. Newer techniques now utilise combined chemo-radiotherapy in an attempt to enhance the sensitivity of tumour cells to radiation[3].

Post-treatment morbidity in cancer patients can be extensive owing to the toxic effects of chemotherapy on bone marrow, surgical deformity and