When Innovation meets Imagination:

Looking to the Future of Oral Cancer Treatment

by

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Abstract

Oral squamous cell carcinoma (OSCC) is a lethal and deforming disease of rising global significance. Whilst advances in diagnosis and management have improved many aspects of quality of life, around 50% of patients die from progressive, recurrent or metastatic disease. The authors of this paper look towards the future of cancer therapy, combining innovative and imaginative approaches, to hypothesize new, effective tumour-targeting therapies that reduce deleterious side-effects from contemporary invasive and ablative treatment. Ultimately, they pose the question, can we envisage a time when terminal diseases are regarded as chronic, manageable conditions?

Introduction

Cancer is one of the main causes of premature mortality in the World today. During 2020, around 20 million newly diagnosed cases and 10 million deaths were estimated to have occurred. As dental practitioners, we are only too aware that oral squamous cell carcinoma (OSCC), the most frequent form of mouth cancer, remains a lethal and deforming disease in contemporary practice exhibiting rising incidence and posing a significant burden to our patients; each year over 300,000 new cases are diagnosed worldwide. Despite advances in disease management, and ability to detect early signs of OSCC during routine oral examination, 5-year survival rates persist at around 50% primarily due to late presentation of patients with advanced stage disease[1].

Our ability to improve patient mortality and reduce disease morbidity requires enhanced public and professional awareness of OSCC risk, delivery of effective preventive strategies targeting 'high-risk' patients and populations and, ideally, supported by improvements in diagnostic technique and better coordinated early-stage treatment interventions[2].

The authors of this article, T C Ng, a dental practitioner and inventor who has designed innovative oral hygiene devices and advanced robotic drill mechanisms to assist both in space exploration (the Beagle 2 Mars explorer) and in the investigation of the tombs of Egypt, and Peter Thomson, an oral and maxillofacial surgeon and oncology researcher, first met in Hong Kong in 2017 and discovered a shared passion to improve outcomes for cancer care and to try to reduce treatment morbidities for our patients; Figure 1.

In this paper, the authors briefly review our understanding of cancer biology and contemporary clinical management approaches before looking more innovatively and, hopefully, a little imaginatively towards future approaches to cancer care. Whilst innovation is based upon improvement and development of ideas and technology, imaginative concepts are perhaps best considered to arise from creative attempts to confront and resolve problems in new ways.

Cancer Biology

Originally termed 'cancer' due to the microscopically observed 'crab-like' projections of abnormal epithelial tissue invading subjacent connective tissue, malignant tumour formation involves a complex, multi-stage disruption to the normally well-controlled processes of cell proliferation, differentiation and development. Tumour initiation and subsequent progression results from tissue damage by extraneous physical, chemical or biological carcinogens, or from unpredictable, spontaneous mutation. Uncontrolled tumour 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. The systemic nature of cancer is increasingly

recognized as an early feature of disease progression. Ultimately, a battle for nutritional resource and biological survival ensues between tumour and host. In the absence of effective treatment intervention, the host is progressively weakened by the ever-increasing tumour burden giving rise to classical signs of advanced malignancy including cachexia, anaemia and muscle wasting, before progressing to organ failure and death. Whilst Table 1 summarises the classic, biological characteristics of epithelial malignancy, it is increasingly recognised that tumours become highly heterogenous in nature during the progression stage creating mixed cell populations with varying molecular identity and thus increased resistance to treatment [1,3].

Cancer Treatment

Contemporary cancer treatments are based upon the aggressive treatment modalities of ablative surgery, radiotherapy and/or chemotherapy. These are increasingly combined in specific regimes, designed and prescribed in multi-disciplinary specialist cancer clinics, in attempts to target the multiple pathways inherent in tumour progression and thereby enhance efficacy[1].

Conventional surgery requires the use of appropriate access techniques, such as the lower lip split and swing mandibulectomy, to facilitate full tumour visualisation allowing resection with a margin of adjacent normal tissue in anticipation of local tissue invasion, together with excision of draining lymph nodes via neck dissection to address metastatic spread; successful tumour clearance can only be confirmed upon subsequent histopathological tissue examination. The application of ionising radiation as localised radiotherapy to the primary tumour site preferentially destroys rapidly proliferating tumour tissue, albeit at the expense of damaging normal tissue, and may also be utilised post-surgery to ‘sterilize’ the operative field of residual tumour. Chemotherapy offers similar effect, targeting actively dividing cells to eliminate tumours whilst allowing normal cells to repair, but is of course administered systemically with significant resultant morbidity. Increasingly, combination chemo-radiotherapy is utilised to enhance the sensitivity of tumour cells to radiation. Table 2 lists the important principles of oral cancer management[1].

Post-treatment morbidity in oral cancer patients can thus be extensive owing to the toxic effects of chemotherapy, especially affecting bone marrow, gastro-intestinal tract and skin, orofacial surgical deformity and scarring, and long-term local tissue damage from ionising radiation. Whilst newer techniques such as sentinel lymph node biopsy to identify low volume metastatic disease and intensity-modulated radiotherapy (IMRT) or stereotactic ablative radiotherapy (SABR) have delivered more targeted treatment and reduced damage to adjacent healthy tissue, tumour resistance and treatment failure remain problematic[1,3,4].

In general, the earlier a tumour is diagnosed and treated, the better the outcome. Individual patient prognosis is highly dependent upon the stage of disease and the effectiveness of treatment. Unfortunately, despite significant advances in diagnosis and management, many patients with oral

malignancy die from progression of their primary tumours or from uncontrolled and widespread metastatic disease. Increasingly, it is recognised that individual host/tumour relationships are unique and highly patient-specific and may well hold the key to improving treatment outcomes[1].

Innovative Treatment Concepts

Future approaches to patient management must therefore rely upon novel and transdisciplinary approaches to optimise therapeutic impact. A variety of treatment strategies, ideally marshalling biological and systemic therapies will be required, tailored individually using genomic analysis and based upon more precise assessment of patient risk.

Table 3 summarizes innovative approaches to cancer treatment. Whilst many remain experimental in nature, they are designed to enhance diagnosis, improve efficacy in targeting primary tumours and treating widespread metastatic disease, and thereby should help to address limitations in conventional therapies and reduce treatment morbidities[3-5].

Early Diagnosis and Treatment Intervention

Following mapping of the human genome 20-years ago, the concept of analysing an individual person's DNA to identify mutations that risk cancer development has evolved rapidly; such pre-clinical, biomolecular diagnoses may facilitate screening of 'high-risk' individuals and preventive treatment interventions. A number of cancer gene therapies have now been proposed including the activation of chemo-sensitising genes, expression of tumour suppressor and antitumour immune response genes, as well as targeted silencing of oncogenes[3,4].

Delivering personalized cancer therapy based upon tumour and patient-specific genetic information also offers clinicians opportunities to target specific mutations with appropriate immunotherapies, including immune checkpoint inhibitors, monoclonal antibodies, cancer vaccines, and immune system modulators. In adoptive cell transfer (ACT) techniques, utilised for example in recurrent leukaemia or aggressive lymphoma, T-lymphocytes with high activity are directly isolated from a patient's blood, re-engineered *in vitro* to express chimaeric antigen receptors (CAR), and the re-infused to specifically target identifiable cancer cell antigens[3,6].

Contemporary cancer diagnosis is still based upon invasive tissue biopsy to determine tumour histopathology and then patient imaging to accurately stage disease status. Unfortunately, many malignancies are only recognised late in their clinical presentation and often at advanced, incurable disease stages. Attention has turned, therefore, to the earlier identification of tumour biomarkers using less invasive techniques.

'Liquid biopsies' have been trialled to identify and characterise circulating tumour cells (CTCs), malignant cells released from the primary tumour into the peripheral circulation, providing early detection of metastatic cancer. CTCs can provide cytological and molecular information that is highly

patient and tumour specific and may act as biomarkers to predict disease progression and tumour recurrence. In addition, cellular remnants such as DNA, RNA, proteins, lipids and extracellular vesicles (EVs) or exosomes, the latter shed from tumour cells and thought to drive tumour microenvironment development and metastatic progression, have all been proposed as potential early markers of cancer and possible therapeutic targets[5].

Precision Tumour Surgery

Precision surgery is designed to optimize delivery of an effective individualised treatment, whilst minimising therapy-related side effects. Whilst technological advances have undoubtedly improved anaesthetic, peri-operative and rehabilitative care for patients undergoing surgery, refinements in surgical technique have proved disappointing thus far in delivering significantly improved cancer cure rates. Minimal access surgery, for example, perhaps best illustrated by trans-oral laser surgery or more recently trans-oral robotic surgery for oropharyngeal cancer, reduces scarring and morbidity post-operatively with clinical outcomes comparing favourably with conventional radiotherapy, but these are expensive, technically demanding treatments that often still require adjuvant post-operative chemoradiotherapy for disease control, albeit at reduced dosages[7,8].

In recent years, thermal ablation of tumours, most effectively hyperthermia delivered by radiofrequency, microwave, laser or magnetic ablation have shown promise in selective destruction of cancer cells. Laser surgery has a particular advantage in delivering precisely focused and powerful laser beams that enhance efficacy and safety. Minimally invasive treatment by laser at an early stage of cancer progression can be curative, delivering effective tumour resection or destruction whilst ensuring minimal collateral damage to adjacent, often vital, tissue structures[7,10,11].

Dealing with Systemic Disease

Biocompatible nanoparticles (ranging from 1 to 1,000nm in size) possess physicochemical properties that allow encapsulation of specific anti-tumour agents, including both chemical and physical agents, improved biocompatibility and targeted delivery specifically at tumour sites. Such systems improve the low specificity and toxicity of systemic chemotherapy drugs[3].

Oxidative stress and radical oxygen species production throughout the body are known to result from carcinogen activity. Natural antioxidant agents, such as vitamins, alkaloids, carotenoids and curcumin are known to exhibit significant anti-proliferative and pro-apoptopic properties and are increasingly used as complementary approaches to modern cancer therapy due to the apparent absence of adverse effects on normal cells at therapeutic doses[3].

Artificial Intelligence

Cancer is a complex disease. Successful patient management requires assimilation of large amounts of information relating to both diagnostic and therapeutic procedures. Artificial intelligence and machine learning technologies are increasingly employed to manage ‘big data’ sets and assist in the prediction of treatment efficacy, clinical outcome, disease recurrence and survival. Such tools offer real

opportunities not only for a more-timely introduction of multimodality treatment but also in excluding the use of aggressive interventions if deemed unwarranted. We have already trialled the use of deep learning to predict oral cancer prognosis and malignant transformation of potentially malignant disorders with some promising results; more work is required to translate this into clinically applicable management tools[3,12,13].

Imaginative Treatment Concepts

Philosophers have long believed that human beings possess an inherent ability to create anything that they imagine. Whilst not wishing to embark on a complex, philosophical debate, the authors of this paper certainly subscribe to the view that imaginative concepts remain central to the creative endeavours underpinning scientific discovery[14].

How then can we harness an imaginative approach to the design and functionality of future cancer therapies? In Table 4, we hypothesize four theoretical treatment concepts, highlighting their proposed methodologies and our ideal treatment outcomes. These imaginative treatments aim to address improvements in early disease recognition and intervention, deliver more precise tumour surgery, improve the control of lymphatic disease, and ensure effective management of systemic disease.

Imagine if we could reliably highlight abnormal, dysmature tissue (epithelial dysplastic change) during potentially malignant disease or identify early-stage carcinogenesis using 'tumour paint' (such as proposed with the fluorescent contrast agent 5-Aminolevulinic acid), and then use precision laser surgery to accurately target and destroy abnormal tissue in a 'one-stop' out-patient diagnosis and treatment session[15]?

Imagine if we could harness accurate tumour imaging, even for deep-seated cancers, and utilise robotic endoscopic surgery with a custom-designed 3-dimensional lens to destroy tumour tissue of any size or shape according to its precise geometry whilst preserving embedded vital blood vessels and nerves?

Imagine if we could utilise similar, high-definition imaging to accurately map the draining lymphatic system for each individual patient, determine the detailed relationship between primary tumour and local lymphatic vessels and nodes and then instigate precision metastasis-targeting treatment?

Imagine if we could place an in-dwelling catheter, the 'Martian vein' concept, to first identify and then target CTCs in the peripheral vasculature by biochemical, immunological or physical treatments? Could patients undertake 'tumour dialysis' at home on an intermittent basis to purify and filter out CTCs, tumour micro-emboli and/or tumour DNA thereby minimizing the risk of systemic metastatic disease[16]?

Conclusions

Innovative, imaginative or implausible? Only time will tell. Until then, we hope that this article will be of interest to FDJ readers and stimulate both discussion and debate. As the global burden of cancer continues to rise, future cancer treatments will need to combine precise and effective tumour-targeting therapies with less invasive or destructive treatment, thereby reducing patient morbidity and diminishing treatment side effects. Our aim must be, unquestionably, to improve survival, but also to enhance patients' quality of life and, wherever and whenever possible, transform terminal disease status into a chronic, manageable long-term condition.

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Competing Interests

The authors have filed for patent protections for the 3D geometric lens and the 'Martian vein' concept.

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TABLES

Table 1: Biological Characteristics of Cancer

- Invasive Tumour Arising from Epithelial Lining Tissue
- Accumulation of Multiple Mutations in Cellular DNA
- Complex, Multi-Stage Disruption in Cell Proliferation, Differentiation & Development
- Tumour Initiation & Progression – via Carcinogens or Spontaneous Mutation
- Abnormal, Uncoordinated Tissue Growth - Persists after Initiating Stimuli
- Local Tissue Invasion & Destruction – Nerves, Blood Vessels, Lymphatics
- 'Crab-like' Projections of Abnormal Epithelium into Subjacent Connective Tissue
- Loss of Cell Adhesion, Metastasis & Tumour Seeding
- Tumour / Host Battle for Survival

Table 2: Oral Cancer Management Principles

- Patient Evaluation
- Tumour Diagnosis, Classification & Staging of Disease
- Treatment Planning
- Coordination of Therapeutic Modalities
- Oro-facial Reconstruction & Rehabilitation
- Psychological & Social Support

Table 3: Innovative Approaches to Cancer Therapy

- Gene Therapy to enhance Tumour Suppressor or silence Tumour Promotor Genes
- Immunotherapies: Monoclonal Antibodies, Immune Modulators, T-Lymphocyte Therapy
- Liquid Biopsies to detect and then target Circulating Tumour Cells
- Thermal Tumour Ablation (Hyperthermia)
- Biocompatible Nanoparticles for Precision Chemotherapy
- Antioxidant Therapies
- Artificial Intelligence to Manage 'Big Data' and Characterize Disease Status

Table 4: Imaginative Concepts in Cancer Treatment

Concept	Target	Method	Objective	Outcome
Enhanced Laser Diagnosis & Resection	Potentially Malignant Disease Primary Tumour	Tumour Paint Targeted Laser Surgery	Identification and Elimination of Early-Stage Carcinogenesis	Early Diagnosis of Malignancy Low Morbidity, Curative Treatment
3D Geometric Lens	Primary Tumour Local Tissue Invasion	Geometrically Guided Endoscopic Laser Surgery	Minimally Invasive Technique Preservation of Vital Structures	Precision Surgery Low Morbidity, Curative Treatment
Lymphatic Mapping	Local Lymphatic Spread	Computerised Imaging of Lymphatic System	Removal / Destruction of Lymphatic Metastases	Eradication of Lymphatic Spread
'Martian Vein'	Systemic Disease	Tumour Dialysis	Removal / Destruction of Circulating Tumour Cells	Prevention of Tumour Seeding

FIGURE

Figure 1: Peter Thomson (left) and TC Ng (right), pictured together in discussions in Hong Kong, during 2018.