Ian Burton
Michael F. Klaassen
Editors

Atlas of Extreme Facial Cancer

Challenges and Solutions

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This atlas is dedicated to all our patients who have endured facial cancer and trusted us to find them a solution.

Foreword

The challenge of healthcare delivery in the twenty-first century is rapidly increasing in a world of widening disparities between the haves and the have nots. Steadily rising costs of modern medicine across all communities in the face of the multipronged attacks of financial constraints, restricted access to treatment, against a background of the much larger issues of climate change and its global effects means we are likely to see across the board more advanced disease presenting later. The unprecedented complication of the Covid-19 pandemic and its impact of health service delivery only serves to exacerbate this risk.

Advanced head and neck skin tumours present a major burden to both the individual afflicted and their family as well as the medical professionals called on to manage these complex cases. By dint of these tumours frequently extending across anatomical subregions, their management often requires complex interactions between the conventional silos of modern medical and surgical practice.

This atlas superbly brings together all the elements of the multidisciplinary team necessary to assess and treat those presenting with extreme facial cancer. Recognizing that total management does not begin and end with medical and surgical specialists, this text broadens the discussion to include the role of the speech and swallowing therapists, dental and maxillofacial rehabilitation, as well as the epidemiology and biology of these most extreme cases.

Drawing together expertise across generations and from a number of continents the authors are to be congratulated for having successfully identified pathways available in most health systems to treat, reconstruct and where necessary palliate patients with extreme facial tumours.

Mark Moore,
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Preface

Some years ago I realized there were many excellent books published about the common-or-garden facial cancers that we encounter in everyday clinical practice. There seemed to be an absence of a book which focussed on the extreme cases, which, although rare, challenge the patient, their families and the various clinical teams trying to manage them. Over 30 years I had worked as a member of various head and neck cancer teams in the UK, Australia and New Zealand documenting a significant number of extreme facial cancer cases. By definition these are cases which require complex surgery to resect and reconstruct the problem, need adjuvant oncological therapies and ultimately may be life-threatening. The recorded cases, some of which had prolonged follow-up, provided an initial database on which to create an Atlas, illustrating the fundamental principles of plastic surgery developed by Gillies and others over a hundred years ago. Sir Harold Gillies (1882–1960) also emphasized the critical importance of the Team Concept in Cancer Surgery. Therefore I set about inviting various team members that I had either worked with or got to know through mutual interests in the field of head and neck cancer and encouraged them to contribute chapters to the Atlas.

This has been a challenge in itself—cajoling busy professionals to devote precious time to complete their chapters but we succeeded. A broad range of specialists from oncological to reconstructive surgeons, anaesthetists, radiologists, pathologists, speech and swallowing therapists, anatomists, scientists and epidemiologists, all familiar with the challenges of facial cancer, have come together in one multidisciplinary book. My appreciation of the different but key roles that my colleagues continue to make to this field of modern medicine has been an inspiration. We have been purposefully inclusive and also keen to consider innovation and future concepts such as the role of cancer stem cells, digital technology for prosthetic rehabilitation and modern morphing technologies.

With authors from around the world including Great Britain, China, South America, Australia and New Zealand this Atlas is truly an international effort, supported by the expert professionalism of the Springer Publishing Company. Facial cancer will continue to be a clinical challenge but the opportunities for either cure or palliation are many and it is important for all of us to highlight and share them. I am grateful to my co-editors, colleague and friend Dr. Ian Burton, FRACS, for his eagle eye and grasp of the English language.

Auckland, New Zealand — Michael F. Klaassen
Gisborne, New Zealand — Ian Burton

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The editors Burton and Klaassen wish to thank the following surgeons who contributed to the early concepts, patient data and vision for this ATLAS. They include Dr Nicholas Otte [surgical trainee of Perth, Australia], Dr Nita Ling [plastic surgeon of Townsville, Australia] and Dr Steve Evans [maxillofacial surgeon of Hamilton, New Zealand]. We also acknowledge the efforts and professionalism of the Springer publishing team as well as the patience of our wives Sue Burton and Karen Klaassen.

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Part I

Epidemiology, Science, and Anatomical Concepts

The Skin Cancer Epidemic

Michael F. Klaassen, Ian Burton, Earle Brown,
Patrick J. Beehan, and Swee T. Tan

Core Messages

- High-risk cancers of the face are best managed by experienced plastic surgeons in a multidisciplinary setting.
- These cancers are relatively rare compared to the very common occurrence of skin cancer as a prevalent cancer in the general population, but require a unique surgical skill set.
- Accurate diagnosis and a precise surgical plan of management should be co-ordinated with adjuvant therapies including radiation, medical, and immunotherapy oncological protocols.

1 Introduction

Australia and New Zealand with a combined population of about 31 million citizens, many of Celtic heritage, who live in a region with very high solar ultraviolet index, are characterised by the highest incidence of skin cancer in the world. These cancers result in a significant health, economic, and social burden.

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Two in three people in Australia and New Zealand will develop skin cancer in their lifetime [1]. While the majority of these are the relatively indolent and slow-growing basal cell carcinomas (BCCs), there are a certain number of more aggressive skin cancers that present to plastic surgeons and other specialists. These include high-grade squamous cell carcinomas (SCCs), de-differentiated (basosquamous) carcinomas, malignant melanoma (MM), and rarer entities such as Merkel cell carcinoma, sebaceous carcinoma, adnexal carcinoma, and sarcoma. Cancer of the upper aerodigestive tract arising from the mucosal surface is also a significant entity affecting the head and neck. A distinctive feature of extreme facial cancers is perineural spread along the cranial nerves.

Australia and New Zealand have the highest incidence of skin cancer in the world. In 2014, Australia recorded 959,243 Medicare claims for the treatment of non-melanoma skin cancer (NMSC). This is an underestimate. The annual incidence of NMSC in the USA has been recorded as 3.5 million [2], with a population in 2020 of 331 million—one tenth the incidence of NMSC in Australia and New Zealand.

The risk of developing skin cancer in Australia and New Zealand is greater for men than for women (70% versus 58%). Deaths from skin cancer exceed those caused by road trauma with 2162 recorded for Australia in 2015, 1520 of which were attributed to MM. In 2017, 310 deaths were caused by MM in New Zealand.

Although mortality rates of skin cancer have been increasing in Australia and New Zealand since 2000, recent trends suggest stabilization of the numbers for those citizens <45 years of age. This is a result of reduced ultraviolet exposure resulting from successful and very prominent public education programs.

The ultraviolet levels in New Zealand are very high especially in summer months. The ozone "hole" over Antarctica, Celtic skin types, and a sun-seeking outdoor lifestyle of the population, all contribute to the high incidence of skin cancer. The National Institute of Water and Atmospheric

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Research has shown that ultraviolet levels are 40% higher in New Zealand than at a corresponding latitude in the northern hemisphere [3]. The highest levels of annual ultraviolet exposure in New Zealand are in the Eastern Bay of Plenty region of the North Island, where the lead author (MFK) has provided a provincial plastic surgery service for the last decade. This in part triggered his interest in writing about the extreme forms of facial skin cancer. The second author (IB), a general surgeon practicing for over 30 years in a similar high-ultraviolet exposure regions (Gisborne, East Cape), has also managed patients with skin cancers affecting the face and other body sites, during his long surgical career.

The pathogenesis and molecular biology of extreme facial cancer are well detailed in later chapters by pathologists and research scientists. It involves genetic predisposition and solar ultraviolet radiation damage as well as complex mutations in tumor suppressor genes. There has been a paradigm shift in the theories of oncogenesis involving complex molecular pathways and the role of cancer stem cells.

From a day-to-day clinical management perspective, it is important to be aware of the risk stratification of skin cancers. BCCs with a morphoeic (sclerosing) histological pattern have a much higher risk of local recurrence and therefore require wider excision margins than the standard 4 mm. SCCs with poor histological differentiation and perineural and/or lymphovascular invasion have a predicted metastatic risk of 37% compared to the 0.3% risk for low-risk lesions in the head and neck [4]. Perineural spread caused by head and neck cancer is most often caused by skin SCC, and a high index of suspicion is needed. This also applies to radiological imaging studies of such patients [see Chap. 5 "The Team Approach in Cancer Care" on Applied Anatomy]. MM, the third most common skin cancer in Australia and New Zealand, is responsible for almost 2000 deaths per annum.

2 Why Do Patients Present with Extreme Facial Cancer?

This is perhaps the most important question in this chapter, given the knowledge and expertise in the management of skin cancer generally and the public awareness of this common acquired disease. The reasons are multiple and include personal fear and social isolation, cultural practices such as chewing of carcinogens, lifestyle and workstyle practices, initial mis-diagnosis and or mis-management, specific tumour characteristics, immunosuppression, and/or previous radiation therapy.

All skin cancers of the human face start as small tumours.

Figure 1 shows a typical BCC of the face in a middle-aged woman, which was completely excised and repaired with a postauricular full-thickness skin graft.

Figure 2 shows a 71-year-old man with an infiltrating micronodular BCC of his left infraorbital region, widely excised and immediately repaired with a Mustardé cheek rotation flap. The final image shows the result at 4 years, when he was re-referred with an SCC on his right eyebrow.

Figure 3 shows the extreme disfiguring appearance of a locally advanced BCC in an elderly man who neglected this cancer because of his fear. He was eventually encouraged to seek specialist attention by his wife, who was concerned about food, drink, and saliva spilling out of his left cheek. Sadly, the BCC was very extensive with infiltration of the facial soft tissues and skeleton and was considered inoperable. Appropriate palliative care was provided.

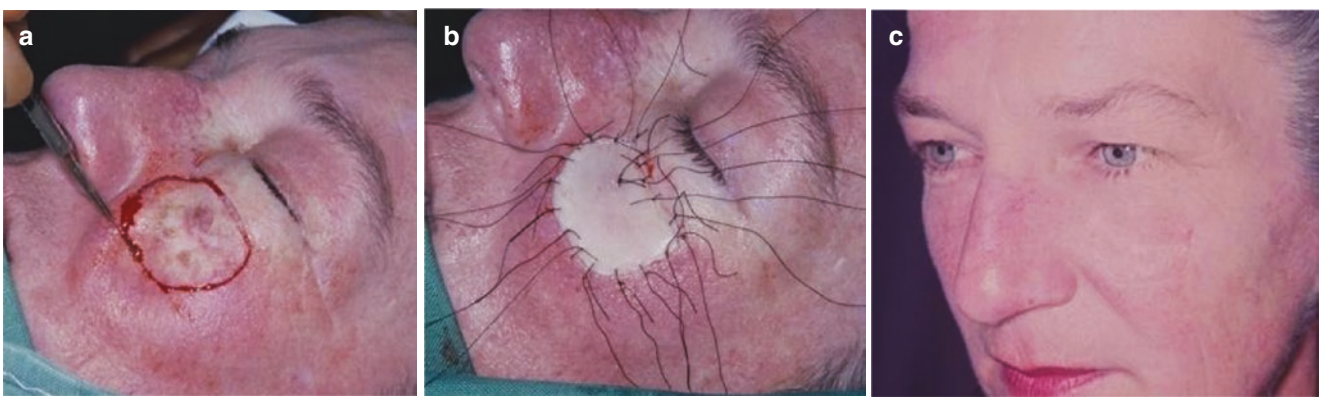

Fig. 1 (**a**–**c**) An infiltrating BCC of the left mid-cheek treated by the late Sir William Manchester (1913–2001) in the 1960s with wide excision and a post-auricular full-thickness graft

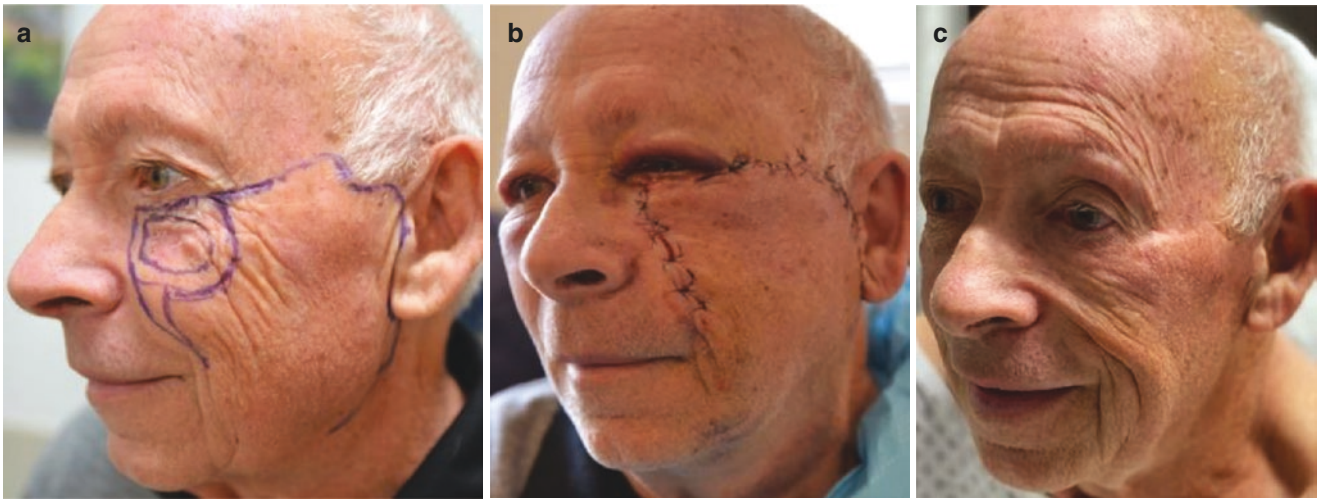

Fig. 2 (**a**–**c**) A case of the lead author – infiltrating BCC of the left infraorbital region widely excised and repaired with a Mustardé cheek rotation flap at 3 days and result at 4 years

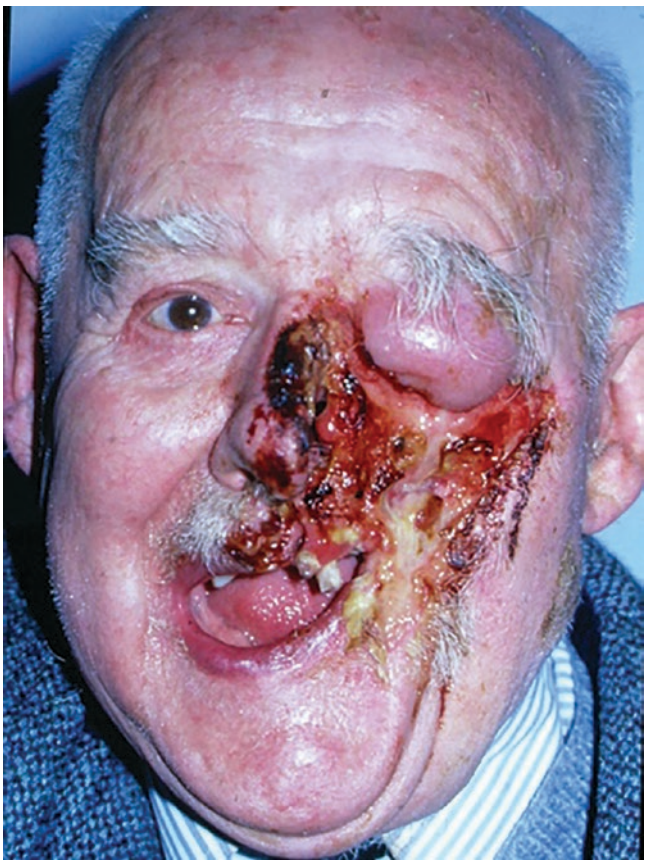

Fig. 3 A neglected inoperable BCC with extensive involvement of the left hemi-face and invading the left maxilla and orbit in an elderly retired chemist seen by the lead author during his post-fellowship training in southern England circa 1990

3 Alternative Medical Misadventure: A Salutary Lesson

A 65-year-old woman sought advice from an alternative medicine practitioner regarding a 3 cm ulcerated lesion on her scalp who allegedly diagnosed the lesion as an "infected sebaceous cyst" and reassured the patient that it was benign. The patient was commenced on a skin treatment regimen involving the daily application of a herbal poultice and dressing changes. After 6 months of treatment, the lesion had grown to 8 cm and developed a purulent discharge. When the patient's family became concerned that the treatment was ineffective, the alternative medicine practitioner allegedly dismissed these concerns and reiterated that the lesion was benign and advised against seeking conventional medical advice. After 16 months of treatment, the lesion had grown to 20 cm and eroded through the calvarium and involved the dura, confirmed by MRI and CT scans (Fig. 4). The tumour was treated by wide local excision including the underlying skull, the greater wing of sphenoid, and dura. Reconstruction included dural repair with a dura substitute, split rib grafts to span the bony defect, and an overlying latissimus dorsi muscle free flap covered with a split thickness skin graft (Fig. 4).

These four clinical cases contrast the relative simplicity of successfully managing early facial skin cancers, as opposed to only being able to offer palliation in the advanced cases. The third and fourth cases clearly illustrate the oncological and reconstructive challenges of the neglected skin cancer. A case report of five patients from Hungary in 2011 shows that delays in the diagnosis and late presentation are usually because of the patient's fears of the diagnosis and treatment. In some cases, the patient just becomes accustomed to the usually slow-growing tumour [6].

Dr. Milton Edgerton MD (1928–2018) of Johns Hopkins Hospital and Virginia University considered the problem of advanced BCC in his Hayes Martin Lecture to the American Society of Head and Neck Surgeons in 1982 [7]. Invasion of deep facial tissues by a BCC and especially the mucous membranes is not a trivial matter, and the patient may never again be tumour-free. His case presentation of a young woman treated with radiotherapy in the 1930s for facial acne chronicles the more than 30 years (1949–1980) of multiple complete reconstructions of her nose, cheeks, lips, and chin. One important principle remains: if the destructive effects of the tumour and the surgical treatment result in the removal of one or more major facial features, it is essential that reasonably prompt reconstruction be undertaken.

This is true for non-facial regions as well and was certainly the case in this retired gentleman, shown in Fig. 5, who presented with a large ulcerated BCC of his left posterior shoulder in 1990. The infiltration had extended into the left shoulder joint, and definitive surgical management necessitated a left forequarter amputation. A radial forearm free flap harvested from the amputated extremity and used to repair the extensive soft tissue defect.

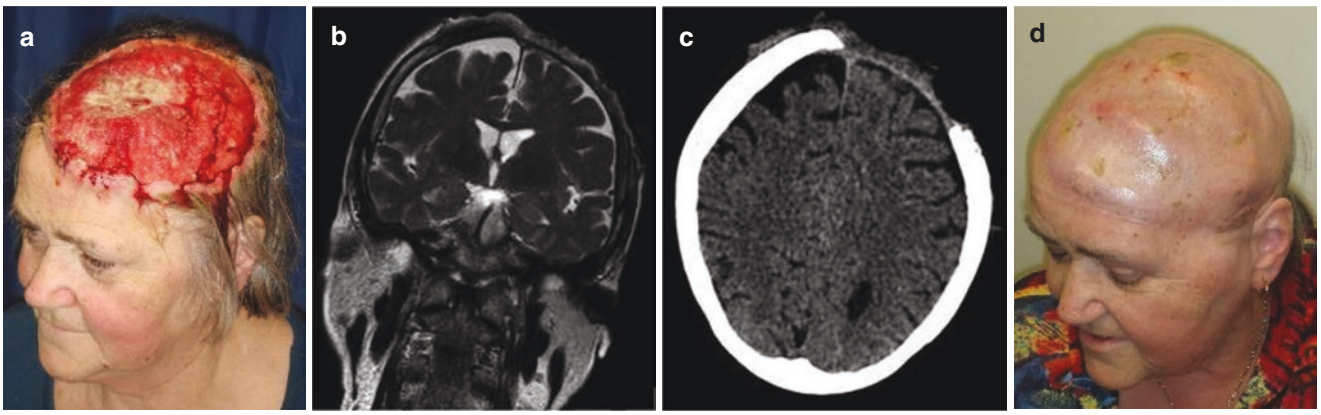

Fig. 4 An extensive scalp SCC with destruction of the soft tissues and underlying skull and invasion of the dura (**a**) also demonstrated on MRI (**b**) and CT (**c**) scans, treated with surgery and adjuvant radiotherapy (**d**). (*Reprinted from* Mistry et al. [5]*; with permission*)

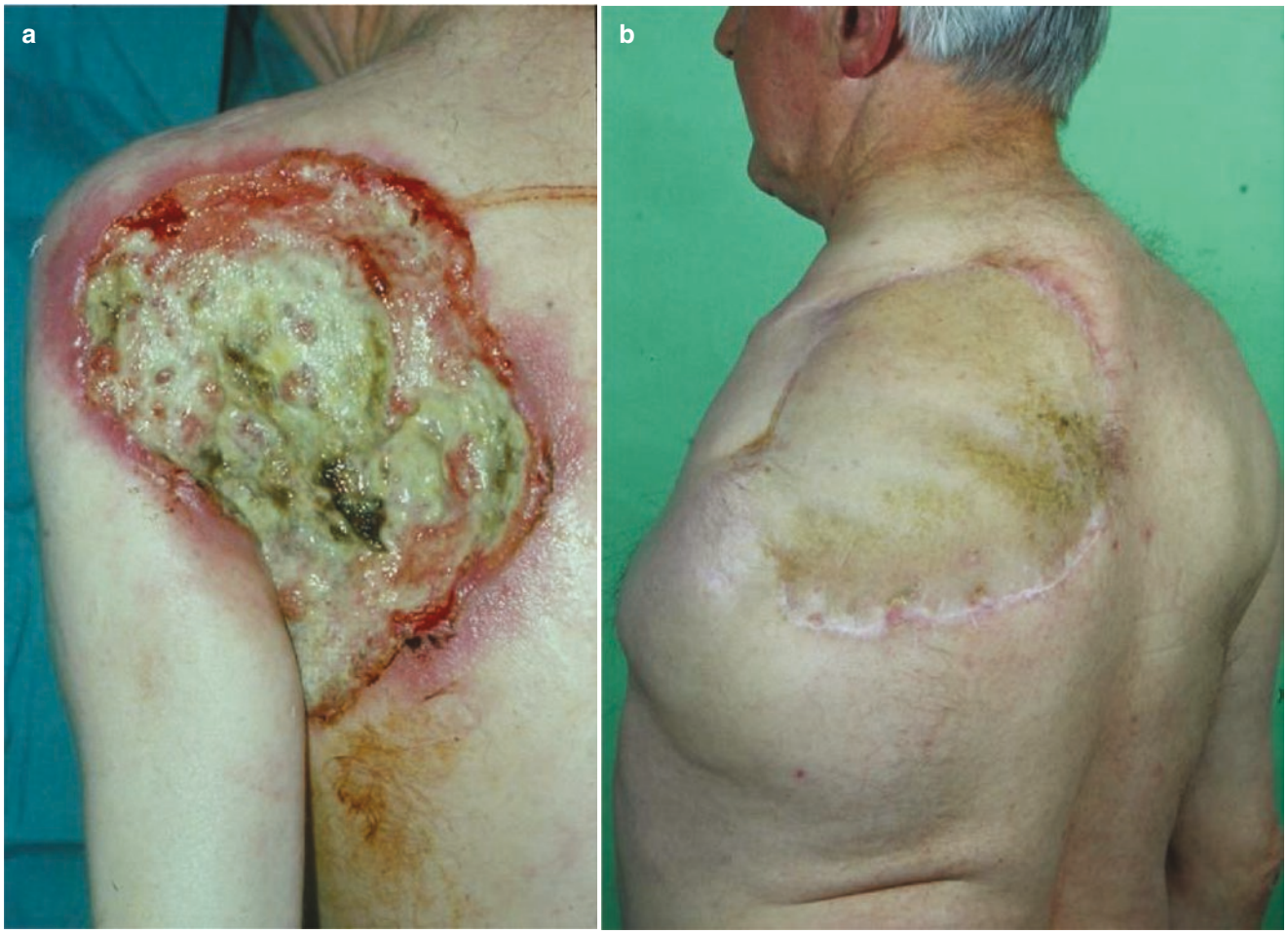

Fig. 5 (**a**, **b**) A case of neglected BCC in a retired London accountant witnessed by the lead author in Southern England circa 1990. The extensive ulcerated tumour invaded the left shoulder joint and required a forequarter amputation and reconstruction with a free radial forearm flap harvested from the amputated left upper extremity

4 Guiding Principles of Surgical Management

Whatever the cancer challenge, the guiding principles (Sir Harold Gillies 1882–1960) for the plastic surgeon remain the same, specifically:

1. Diagnose before you treat.
2. Make a plan and a pattern for this plan (incorporating the choice of reconstruction).
3. Treat the primary defect first.
4. Never let routine methods become your master.
5. Have a lifeboat.
6. Consult other specialists.
7. The aftercare is as important as the planning.

These principles are of course derived from some of the many fundamental truths that became intuitive for pioneers in plastic surgery like Sir Harold Gillies [8].

5 Management/Technique

This 68-year-old man with alcohol addiction (Fig. 6) presented with a neglected, locally advanced ulcerated SCC affecting his left posterior neck. He did not seek medical attention for several months. At one stage, he decided against the wishes of his family to drive to a remote location in North Queensland and attempted to drink himself to death under a eucalyptus tree. When this failed, he drove back to his home city thousands of kilometers away and sought medical attention.

On presentation, the extensive fungating tumor was inhabited by maggots. Physical examination and a CT scan indicated that surgical excision was feasible. A wide local excision along with a radical neck dissection resulted in a significant neck defect which was repaired with a pedicled trapezius myocutaneous flap. The large secondary defect was repaired with a meshed split skin graft. A keystone double advancement flap would also have been a reasonable option for closing the secondary defect. A free flap could have been considered as an alternative reconstructive option, but Professor Michael Poole of Sydney, Australia, who led the surgery for this patient, and the lead author felt that his pre-surgical general condition and relative malnutrition resulting from alcoholism were a contraindication to lengthy microvascular surgery.

Figure 7 shows a 50-year-old woman who presented with an extensive ulcerated lesion of her right upper lip and nasolabial area, which had been treated as an inflammatory lesion for several months. A "delayed" biopsy showed an infiltrating BCC. After margin controlled wide excision and DRAPE (**d**elayed **r**econstruction **a**fter **p**athology **e**xamination) protocol, a term coined by Professor Felix Behan FRACS of Melbourne, Australia, a staged reconstruction of her medial cheek, right alar base, and right upper lip was completed using a cheek rotation local flap, a paramedian forehead local flap, and a lower lip Abbé flap, with satisfactory results.

The 60-year-old man in Fig. 8 presented with extensive facial sun damage and a recurrent Merkel cell carcinoma of his right cheek and required a very extensive hemi-face resection and ipsilateral parotidectomy. A loco-regional flap was considered unreliable, so an ulnar forearm free flap was used for reconstruction. This proximal forearm flap initially described by Dr. Maxwell Lovie FRACS (1939–2000) et al. [9] provided sufficient soft tissue volume compared to the more frequently used radial forearm flap. The patient underwent post-operative adjuvant radiotherapy.

MM rarely presents with extensive facial lesions, but occasionally metastatic spread can pose a challenge, as in this a 70-year-old man (Fig. 9), who developed a nodal metastasis in his left neck, which involved the overlying skin and was adherent to the common carotid artery. In collaboration with the vascular surgeons, a wide local excision and neck dissection including resection of a segment of his carotid artery were performed, with a temporary carotid bypass shunt to preserve brain perfusion. A reversed saphenous vein bypass graft was utilized. The graft was then protected with a pedicled loco-regional pectoralis major myocutaneous flap.

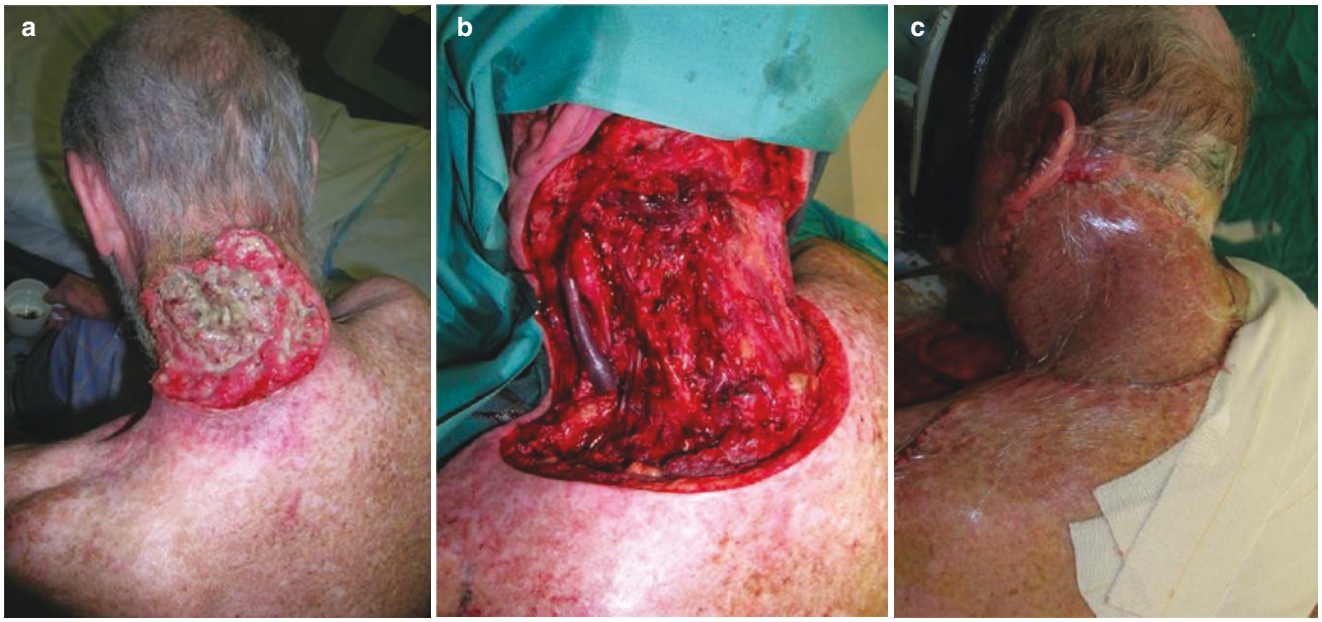

Fig. 6 (**a**–**c**) A neglected fungating SCC of the posterior neck in a 60-year-old gentleman with alcoholism, treated with wide local excision, radical left neck dissection and a pedicled trapezius myocutaneous flap reconstruction

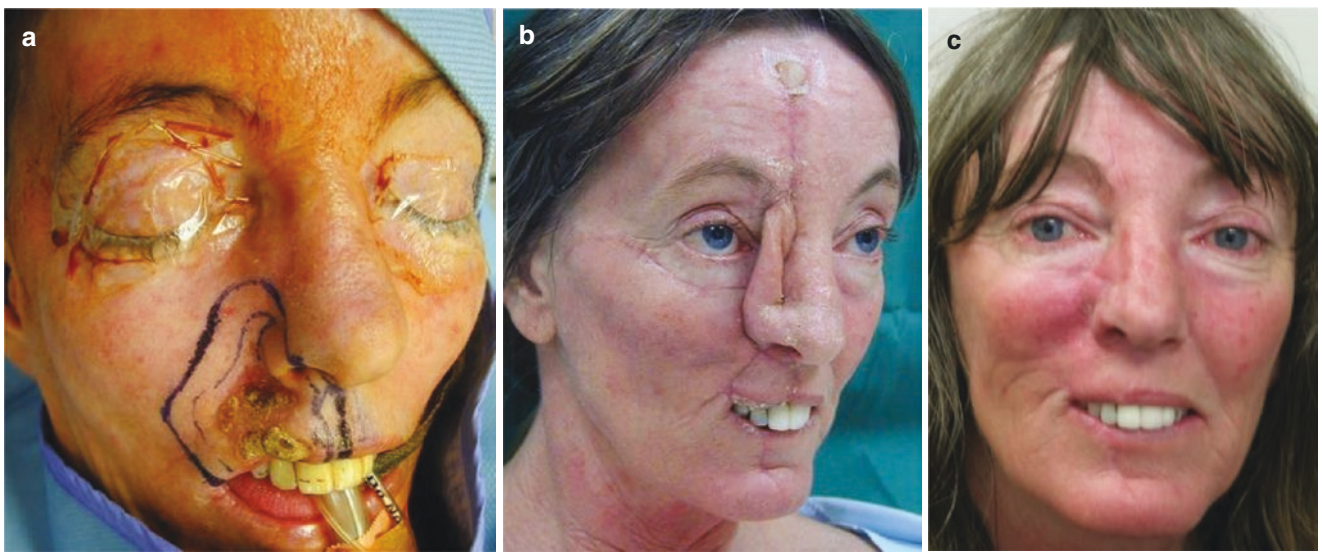

Fig. 7 (**a**–**c**) A misdiagnosed infiltrating BCC of the right upper lip and nasolabial area, widely excised and reconstructed with multiple local flaps (cheek rotation, paramedian forehead and Abbé lower lip-switch flap)

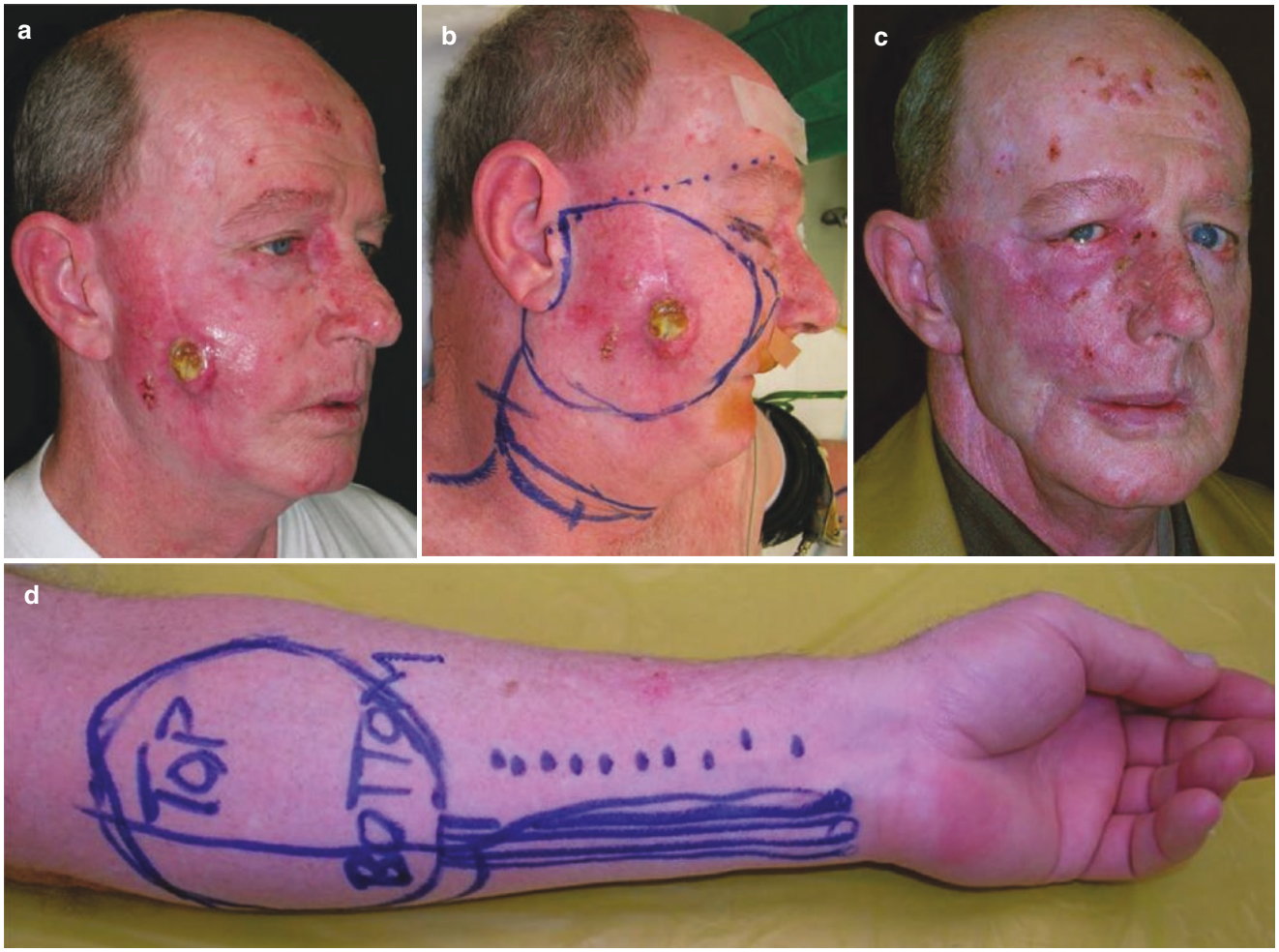

Fig. 8 (**a**–**d**) A recurrent Merkel cell carcinoma on the cheek in a 60-year-old man, was widely excised including a facial nerve-preserving superficial parotidectomy and immediate reconstruction with an ulnar forearm fasciocutaneous free flap, followed by adjuvant radiotherapy

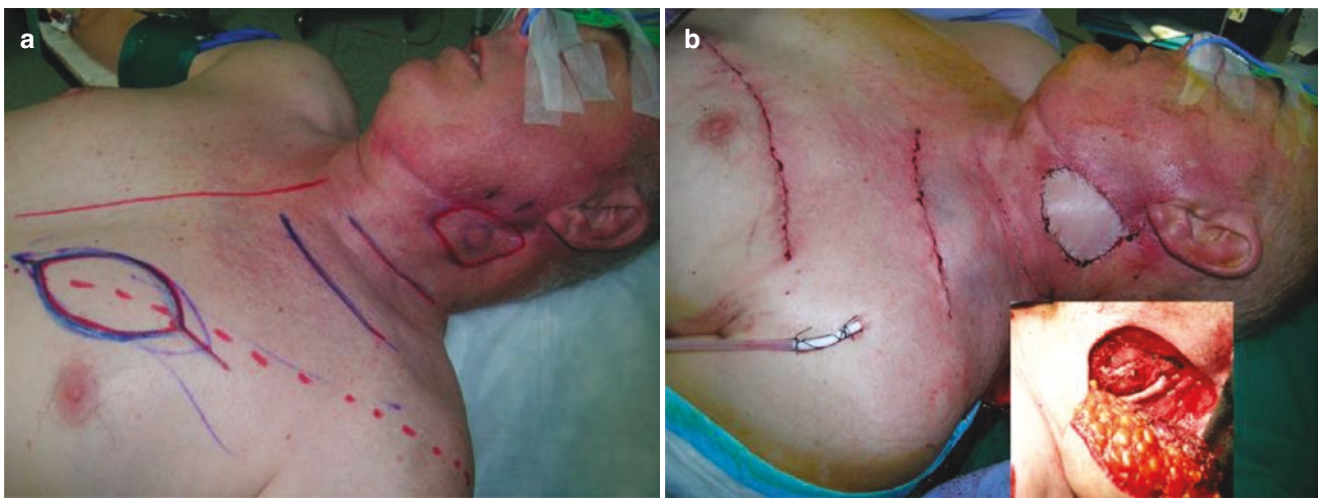

Fig. 9 (**a**, **b**) Metastatic malignant melanoma in a 70-year-old man's left neck adherent to the left common carotid artery. Salvage surgery with local excision, neck dissection, bypass shunt, saphenous vein bypass graft of the excised carotid artery and reconstruction with a pedicled left pectoralis major myocutaneous flap

6 Indications

Innovative reconstruction methods are required when the cancer burden is extensive, the resection defect considerable, and where traditional methods of repair are inadequate.

6.1 Loco-Regional Combined Flaps

This 45-year-old pastor from Papua New Guinea (Fig. 10), with extensive SCC affecting the lips and right cheek caused by longstanding betel nut chewing, was referred to our Interplast Humanitarian team. The betel nut was mixed with an alkali lime powder from crushed seashells to reduce the acidity of the ingestion. Chewing betel nut is a traditional social practice in many Pacific Islands including the Solomon Islands, Papua New Guinea, and Vanuatu. Transfer to Australia or New Zealand for resection and free flap reconstruction was not an option, so the team planned a combination of loco-regional keystone flaps from his left cheek and anterior neck. An opinion was urgently requested by the Interplast Team leader (MFK), from Professor Felix Behan FRACS in Melbourne, Australia, via the Internet. The planned total forehead flap was not required for lining. The secondary defect of his submental region was repaired with a skin graft. The case was lost to follow-up.

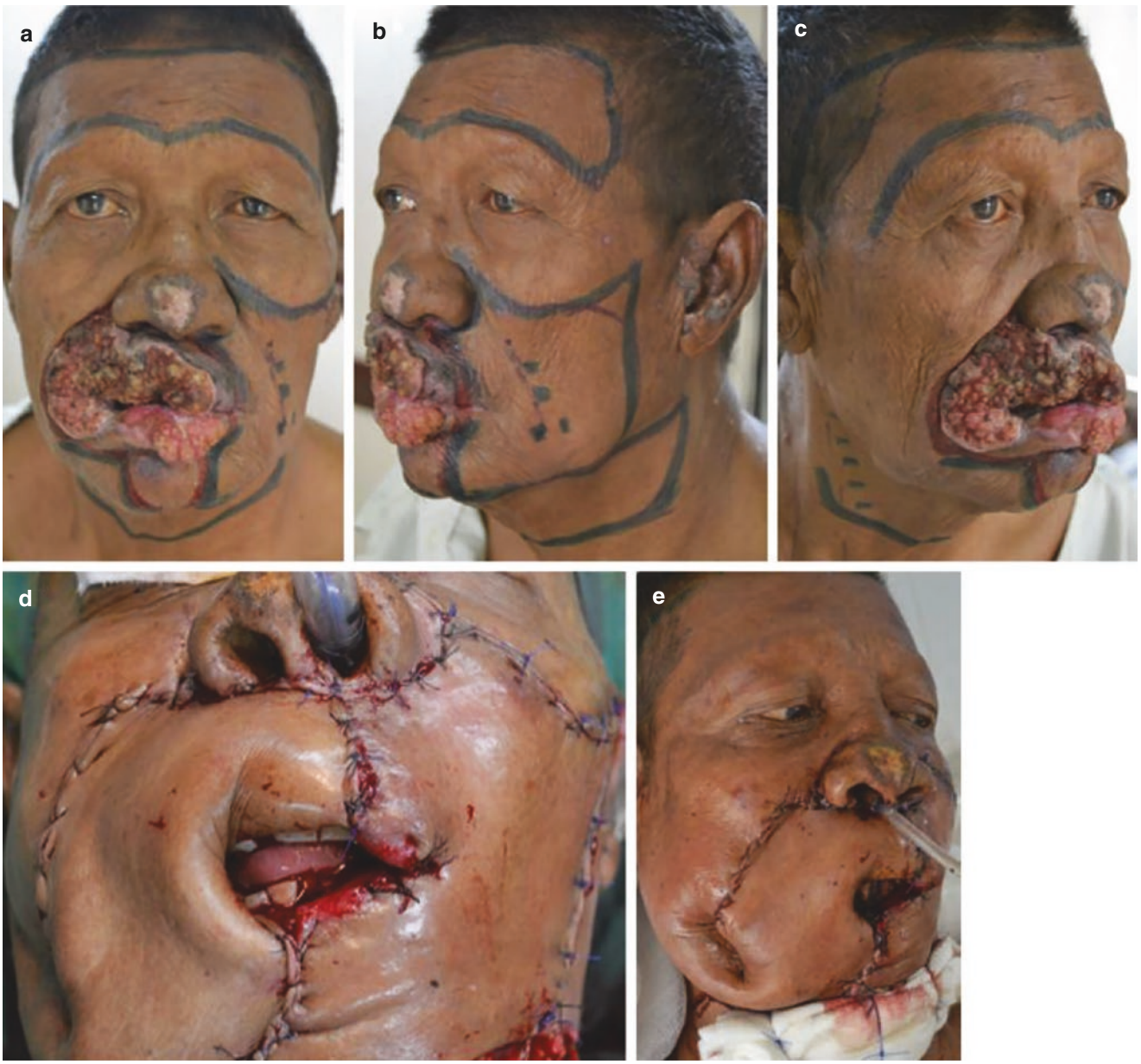

Fig. 10 (**a**–**e**) An extensive perioral SCC of the lips in a 40-year-old Papua New Guinean pastor, referred to a New Zealand based Interplast surgical team. Wide excision in Port Moresby and immediate reconstruction with keystone perforator island loco-regional flaps from the cervicomental and left cheek regions

6.2 Free-Flap Option

This 43-year-old man (Fig. 11) presented to the oral and maxillofacial surgeons with a rapidly growing chondrosarcoma of his right maxilla. An initial right hemimaxillectomy was followed by rapid and aggressive recurrence, which therefore required a wide orbital-heminasal midface resection, immediate reconstruction with a bi-paddled latissimus dorsi myocutaneous free flap, and post-operative adjuvant radiotherapy. Subsequent attempts were made to reconstruct his right heminose defect with a staged forehead flap and bone grafts. He is now 20 years post-treatment and free of disease.

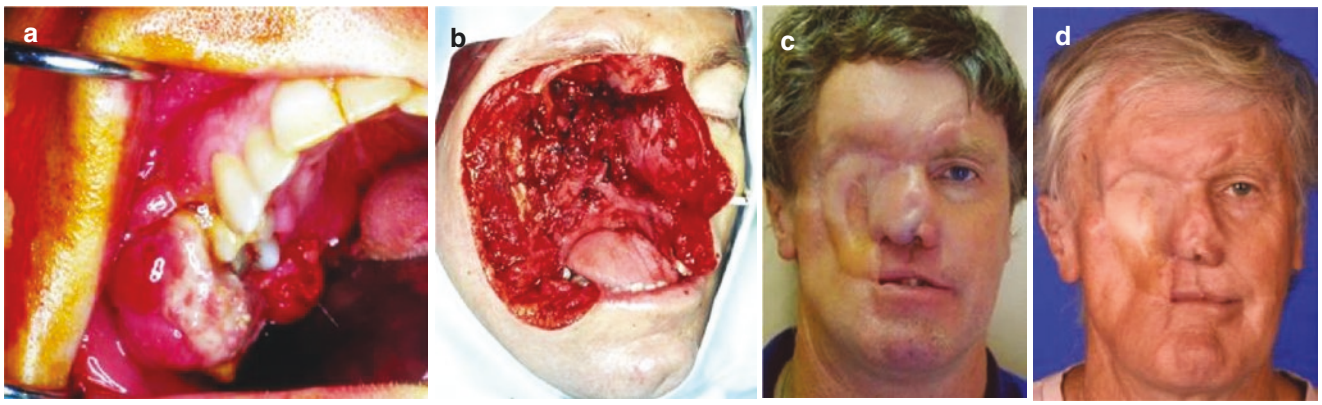

Fig. 11 (**a**–**d**) An aggressive chondrosarcoma of the right maxilla in a 43-year-old man, treated radically with right hemiface resection (right orbit, maxilla and heminose), staged reconstruction with a free bi-paddled latissimus dorsi flap and expanded forehead flap. Alive and well 20 years later

7 Contraindications

There are rare extensive facial cancers that are inoperable as shown in Fig. 3, in an elderly man with longstanding and neglected midface BCC. For some patients, their comorbidities and general medical status as defined by the American Society of Anesthesiology (ASA) Physical Status classification may preclude curative surgery [10]. Professor Michael Poole MD, FRCS (Fig. 12), plastic, craniofacial, and head and neck plastic surgeon in Sydney, Australia with whom the lead author collaborated for 3 years (2004–2006), was a firm and passionate advocate for palliative surgery in selected patients, to improve their quality of life (Fig. 13). The concept of palliative surgery is detailed by Dr. Rafael Acosta-Rojas FRACS, EBOPRAS, in Chap. 15 "Palliative Surgery".

Fig. 12 Professor Michael Poole MD, FRCS – former director of the Oxford Craniofacial Unit, Radcliffe Infirmary, Oxford, UK and plastic surgeon/craniofacial surgeon Sydney, Australia. He mentored the lead author from 1999 to 2008

8 Palliative Surgery as an Option

Figure 13 shows a 78-year-old man with a metastatic skin SCC to the right side of his neck which failed to respond to primary radiotherapy. The fungating tumour resulted in a constant discharge and odour requiring daily dressings, affecting his quality of life significantly. Following a multidisciplinary discussion, the patient was offered and proceeded with salvage surgery. This involved a right radical neck dissection and superficial parotidectomy with wide local excision of the involved overlying skin and amputation of the lower pole of the right ear. The extensive defect was repaired with a large pedicled pectoralis myocutaneous flap (with removal of the nipple). The donor site was closed with an anteriorly based transpositional subcostal fasciocutaneous flap.

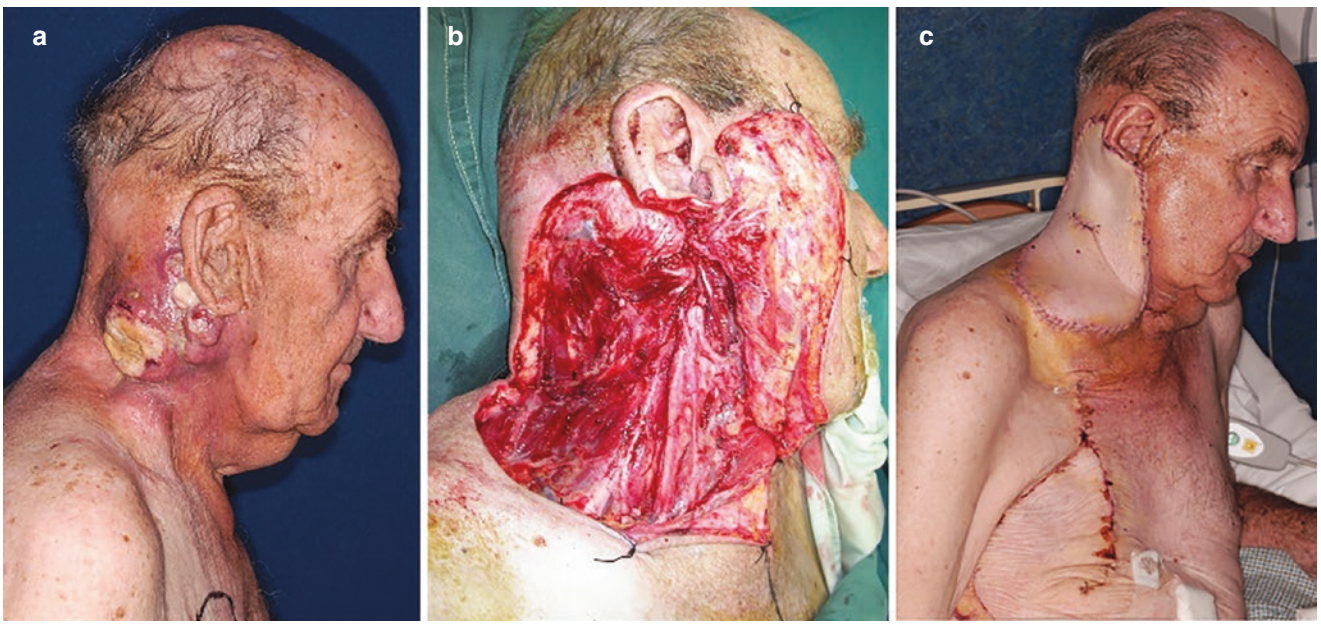

Fig. 13 (**a**–**c**) A 78-year-old man with a fungating metastatic skin SCC on the right side of his neck following primary radiotherapy (**a**), underwent right radical neck dissection and superficial parotidectomy with wide local excision of the involved skin including partial amputation of the right ear (**b**). The resection defect was reconstructed with a large pedicled pectoralis myocutaneous flap and the donor site defect was repaired with a transpositional subcostal fasciocutaneous flap (**c**)

9 Innovations

The keystone perforator island loco-regional flaps of Professor Felix Behan continue to challenge our modern concepts of free flap surgery for major facial cancers. The keystone flap concept was based on clinical observation and the intuition that dermatomal planning of flaps guarantees a supportive vascular supply. Vessels follow nerves. The workhorse perforator flap concept has stood the test of time, for a quarter of a century. The lead author learned this flap from Dr. Simon Donahoe FRACS, a colleague of Behan in Melbourne at the Peter MacCallum Cancer Institute and has been a champion of its application for over a decade [11]. The keystone flap and its variants (Omega, double, Yin-Yang) provide a simple, quick, and reliable option with **pain**-free recovery, **aesthetic** reconstruction, low **complications,** and **economy** of effort and resources: Behan's **PACE acronym**. They are applicable anywhere on the face and neck including the scalp but in the latter experience is required [9]. Professor Behan et al. expand on the application of the keystone flaps in Chap. 9 "Keystone Flap Concepts".

10 Management of Complications

All surgery must balance the advantages of a given method with the risk of treatment. Complications can occur pre-operatively because of poor decision-making and planning (e.g., aspiration pneumonitis or sepsis). Problems may also arise peri-operatively because of imperfect technique, unheralded findings, and anaesthetic emergencies as well as post-operatively. The key post-operative complications include hematoma from bleeding which may compromise flap viability, partial or complete flap necrosis due to vascular insufficiency (most commonly venous outflow problems), injury to vital anatomical structures (e.g., facial nerve, thoracic duct), and sepsis. Incomplete cancer excision or cancer recurrence are also challenging complications. Knowledge of and situational awareness about complications are stressed to plastic surgeon trainees for their professional exam preparation. This becomes a mandatory skill set with consultant experience post final examinations! The philosophy with respect to complications may be a conservative approach, but sometimes a pro-active re-operative approach and salvage are required. The timing and judgment required for this are critical and follow the dictum of Sir Harold Gillies: *Don't do today what can be honorably be put off until tomorrow.* Professor Michael Poole MD, FRCS, from whom the lead author learned so much in the 2000s, would argue that *He who hesitates is lost.*

11 Controversies

Mohs micrographic surgery, a technique popularized by dermatologists in North America and pioneered by a Wisconsin medical student in the 1940s, has been described as a "precise" surgical technique for the treatment of skin cancer. During Mohs surgery, thin layers of cancer-containing skin are serially removed and examined until only cancer-free tissue remains. Although published studies comparing Mohs' surgery with conventional surgical excision claim superior results for BCC specifically, plastic surgeons worldwide question the oncological legitimacy and cost-effectiveness of this approach and its role in extreme facial cancers [12]. The technique is tedious, expensive, painful, and costly, although it may have a role in achieving clear resection margins for certain challenging BCCs, such as those with a morphoeic pattern and/or certain anatomic sites. Chap. 12 "Extreme Cancer of the Periorbital Region" in this Atlas describes cancers of the periorbital region, and Dr. Stephen Ng FRANZCO, an ophthalmic surgeon with a special interest in oculoplastic surgery, who collaborated with the lead author and third author (EB) for that chapter, has significant experience in reconstructing periorbital defects after Mohs micrographic surgery by dermatologists in his region.

12 Conclusion/Summary

Skin cancer is prevalent among the Caucasian population of Australia and New Zealand, with an incidence ten times that of other major developed countries such as the USA. During their careers, plastic surgeons can expect to be confronted with many challenges in the management of skin cancer and occasionally extreme, advanced, and even more challenging cases. Why these rarer cases ever present in the first place is an interesting and vexed question, for which the explanation is often complex and associated with multiple patient personality disorders. It is left for the experts in the field of cancer care to grapple with the challenge and conundrums of extreme facial cancer.

A surgical approach is suggested based on sound surgical principles including a definitive diagnosis, staging, and a multidisciplinary plan of management. Immediate reconstruction with the most appropriate method is ideal, but this may be delayed due to oncological concerns. A range of loco-regional and distant free flap options exist in the surgeon's toolkit, backed up by the adjuvant therapies of radiation and medical oncology. The team includes radiologists, pathologists, prosthetic specialists, specialized nurses, anaesthetists, psychologists, and palliative care specialists as well as surgeons.

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Cancer Stem Cells in the Head and Neck Cancers

Ethan J. Kilmister and Swee T. Tan

Core Messages

- Cancer stem cells (CSCs), the proposed origin of cancer, are present in many cancer types including primary and metastatic cutaneous squamous cell carcinoma and malignant melanoma.
- CSCs are highly tumourigenic, resist conventional therapies and are responsible for loco-regional recurrence and distant metastasis.
- CSCs are regulated by the microenvironment in which the renin-angiotensin system (RAS) plays a vital role.
- The RAS consists of multiple components, its bypass loops that provide redundancies, and convergent signalling pathways that provide crosstalk.
- A novel treatment approach for cancer is by targeting CSCs by regulating the RAS and its related pathways.

1 Models of Cancer

There are two concepts guiding cancer research: (1) the prevailing *clonal evolution model*, also known as the *stochastic model of cancer*, which proposes that normal cells acquire tumourigenicity to become cancer cells by accumulating genetic mutations (Fig. 1a), and (2) the emerging *cancer stem cell (CSC)* concept of cancer, also known as the *hierarchical model of cancer*. The latter proposes CSCs—a small subset of highly tumourigenic cancer cells with embryonic stem cell-like (ESC) properties—as the origin of cancer (Fig. 1b) [1].

The clonal evolution model proposes that all tumour cells are clonally identical and have the same tumour forming ability and propensity for self-renewal (Fig. 1a) [2]. The CSC model proposes that a tumour consists of a heterogenous population of cells with CSCs sitting atop the cellular hierarchy, sustaining tumour cell diversity, tumourigenicity, and metastatic potential [3]. These CSCs divide asymmetrically giving rise to non-tumourigenic cancer cells that form the bulk of the tumour and identical CSCs that are highly tumourigenic, resist conventional therapies and are responsible for metastasis and recurrence (Fig. 1b) [4].

Processes involved in embryonic development are often reactivated under pathological conditions, such as carcinogenesis [5]. Cancer and embryogenesis share multiple common processes such as epithelial-to-mesenchymal transition (EMT) [5]. Another similarity between carcinogenesis and embryogenesis is the shared ability of ESCs and CSCs to undergo indefinite self-renewal and bypass the replicative barrier of 50–60 population doublings before senescence [6]. Both CSCs and ESCs can undergo differentiation giving rise to cells of all lineages and utilise signalling pathways such as the MAPK/ERK, PI3K/AKT, JAK/STAT and Notch pathways [7]. As somatic cells have a low rate of mutations and a relatively short lifespan, it raises the question of how cancer cells acquire so many essential genetic changes seen in ESCs. It is more plausible that cancer arises from CSCs that originate from resident adult stem cells or progenitor cells, which possess higher proliferative capacity and are more prone to mutations. ESCs undergo periods of high rates of clonal proliferation in a highly controlled manner, whereas the proliferation of cancer cells is not controlled. Furthermore, like ESCs, cancer cells can also establish themselves in various tissues in the body [7]. Using embryonic development as a framework for investigation of carcinogenesis could provide novel insights into the understanding and treatment of cancer.

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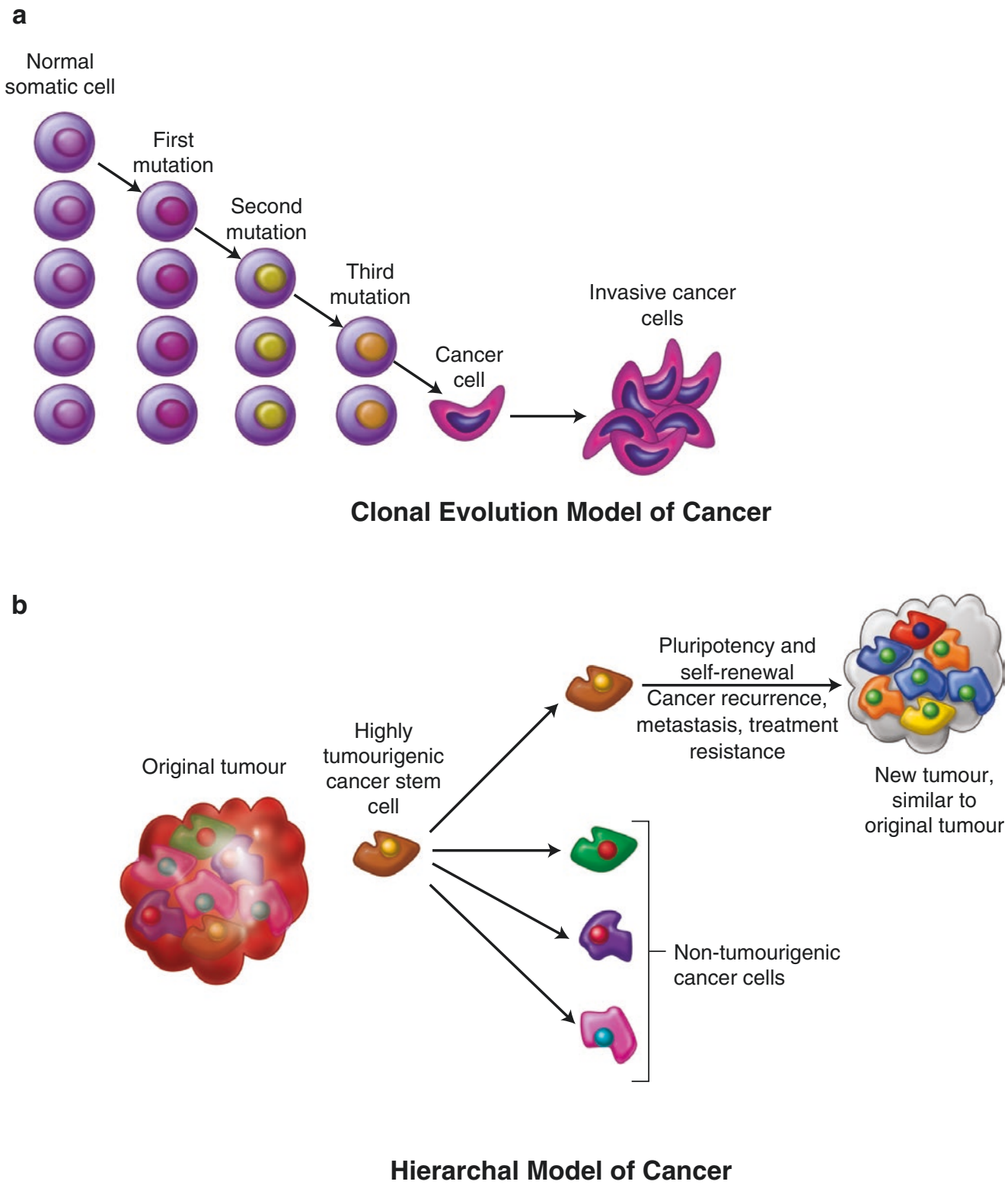

Fig. 1 (**a**) A diagram illustrating the clonal evolution model of cancer. A normal somatic cell acquires oncogenic mutations in a stepwise manner and becomes a cancer cell that clonally expands to form a tumour. (**b**) A diagram illustrating the cancer stem cell (CSC) model of cancer. A highly tumourigenic CSC sitting atop the tumour cellular hierarchy which divides asymmetrically to form non-tumourigenic cancer cells that form the bulk of the tumour, and identical CSCs that form new tumours that are similar to the original tumour

2 Cancer Stem Cells

In 1937, Furth et al. [8] first showed that a single tumour cell from mouse leukaemia could establish a tumour following transplantation into another mouse. Identification of proliferating cells by radio-labelling and autography [9] in the ensuing decades enabled measurements of cell lifespan and the assessment of cellular hierarchy in normal tissues [10]. These methods led to a rapid advancement in stem cell research. In 1960, Pierce [11] demonstrated that teratocarcinomas contained tumourigenic cells that could individually differentiate into multiple differentiated non-tumourigenic cell types, resembling normal development. In 1963, haematopoietic stem cells were discovered, and stem-like cells were reported in multiple haematological malignancies in the ensuing decade [12]. Based on investigations using many other techniques over the subsequent decades, Pierce [13] advanced an early CSC concept—"A concept of neoplasms, based upon development and oncological principles, states that carcinomas are caricatures of tissue renewal, which have a marked capacity for proliferation and a limited capacity for differentiation under normal homeostatic conditions, and of the differentiated, possible benign, progeny of these malignant cells". Evidence supporting the notion that cancer originates from CSCs has been accumulating rapidly over the past two decades. CSCs have now been identified in numerous types of solid cancers affecting all major organ systems [4, 14].

3 Identification of Cancer Stem Cells

CSCs express stemness-associated markers that are present on ESCs and display ESC characteristics such as self-renewal and pluripotency—the ability to differentiate into cells of all lineages [15]. CSCs have been identified in many cancer types [4] including cutaneous SCC (cSCC) and malignant melanoma (MM) by specific markers [16–20]. Their presence is confirmed by functional studies, such as tumoursphere formation assays, organoid systems, and xenotransplantation of sorted tumour cells into immunodeficient mice [21]. Xenograft and teratoma experiments in animals are the gold standard for functional investigations that provide evidence of CSCs, and they remain valuable and perhaps essential for applications such as safety testing of therapies. However, teratoma assay protocols are often vague and inconsistent and are not highly standardised and reproducible [22]. To determine whether a cell population includes pluripotent cells, it is considered sufficient to employ directed or spontaneous differentiation and tumoursphere formation which can be sustained over multiple passages and an analysis of pluripotency marker expression [22]. It has become more acceptable to use stemness-associated markers such as OCT4, SOX2, NANOG, SSEA4 and TRA-1-60, to identify pluripotent cells [23–26].

Many markers that are expressed on ESCs have been used to identify CSCs [27, 28]. CD44 is a cell surface marker with many functions, including the transduction of microenvironmental signals to membrane-associated cytoskeletal proteins and the nucleus, which influences the expression of genes that alter cell functions [29]. As an important regulator of CSC properties including stemness, self-renewal and metastasis, CD44 has been used as a CSC marker [29]. As it is not essential for tumour formation [30], CD44 is now considered a marker of progenitor cells, further down the stem cell hierarchy, rather than an ESC marker [27].

EpCAM, a cell adhesion molecule and a CSC marker, is expressed by nearly all carcinomas [31] including cSCC [31].

The surface marker CD133 has been used to identify CSCs in several solid cancers including glioblastoma [27] and pancreatic cancer and is associated with high tumourigenicity and metastasis [32]. Capan-1, a $CD133^{+}$ pancreatic cancer cell line derived from human pancreatic cancer, recapitulates tumours in a xenograft model [32]. As CD133 is also expressed on more differentiated cancer cells, further down the stem cell hierarchy, and given tumours can also be grown from $CD133^{-}$ cells in xenograft models, it is now considered a progenitor cell marker rather than an ESC marker [27].

Phosphorylated signal transducer and activation of transcription 3 (pSTAT3) proteins have a broad range of functions, including cell cycle signalling, cell survival, pluripotency and self-renewal capability [33, 34]. STAT proteins are activated by cytokines, and they regulate growth factor and cytokine responses [35]. Aberrant STAT3 signalling has been demonstrated in multiple types of head and neck cancers [36]. The role of pSTAT3 in pluripotency is regulated by leukaemia inhibitory factor pathway, resulting in STAT3 translocating into the nucleus and triggering the expression of the ESC markers KLF4, SOX2, SALL4 and c-MYC [37–39]. pSTAT3 is also expressed by more differentiated cells [27].

Yamanaka et al. showed that human [24] and mouse [25] fibroblasts can be induced into an ESC state [24] by introducing the transcription factors OCT4, NANOG, SOX2, KLF4 and c-MYC. Thomson et al. [26] showed that generation of such induced pluripotent stem cells (iPSCs) was also possible with NANOG and LIN28 in place of c-MYC and KLF4. These studies underscore the sufficiency of these stemness-associated markers in generating iPSCs. Expression