Skin Cancer after Organ Transplantation

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Skin Cancer after Organ Transplantation

The SCOPE Collaborative Group

Edited by

Eggert Stockfleth
Claas Ulrich
Charité University Hospital, Berlin, Germany

Sylvie Euvrard
Edouard Herriot Hospital, Lyon, France

Charlotte Proby
University of Dundee, Cancer Research UK
Skin Tumour Laboratory Dundee, Scotland, United Kingdom

Jan-Nico Bouwes Bavinck
Leiden University Medical Centre, Leiden, The Netherlands

Edward K. Geissler
University of Regensburg, Regensburg, Germany

Editorial Consultant:

Petter Gjersvik
University of Oslo, Oslo, Norway

Foreword by Peter Neuhaus

Editors
Eggert Stockfleth, MD, PhD
Charité - Universitätsmedizin Berlin
Klinik für Dermatologie
Venerologie und Allergologie
Charitéplatz 1
10117 Berlin
Germany
eggert.stockfleth@charite.de

Claas Ulrich
Charité - Universitätsmedizin Berlin
Klinik für Dermatologie
Venerologie und Allergologie
Charitéplatz 1
10117 Berlin
Germany
claas.ulrich@charite.de

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Foreword

The life-promoting and life-enhancing benefits of solid organ transplantation are a major and fascinating medical advance, but come at the cost of the lifelong immunosuppression needed to prevent rejection of the donated organ. This induction and maintenance of impaired immunological surveillance is paralleled by significant increases in the incidence of specific cancers, of which skin cancers are numerically way out in front. Prolonged waiting times for organ transplantation, an increasing average age of recipients, and the improving long-term graft and patient survival are closely related to this trend towards steadily increasing rates of post-transplant malignancies and have shifted the concerns of the global transplant community towards the possibilities of post-transplant cancer.

Already the most common cancer in fair-skinned populations, keratinocyte skin cancers are increased a further 100 fold in organ transplant recipients.

Individual high-risk patients demonstrate accelerated carcinogenesis and may develop very large numbers of (predominantly) squamous cell carcinomas, tumours that are more likely to behave aggressively or metastasize in the context of a suppressed immune system.

This book explores the pathogenesis of transplant skin malignancies, including the immunological basis and contribution from specific drugs. Experts in the field recommend management strategies for preventing and treating transplant skin malignancies, with always an emphasis on a multidisciplinary approach. As scientists and clinicians strive together to develop effective pathophysiological concepts and clinical strategies in the face of this accelerated carcinogenesis, there is a real opportunity not only for advances in the treatment of transplant-related skin malignancies but also for translating these findings into effective skin cancer control in the general population.

Following the age of striving for sufficient prevention of acute rejection by developing ever more effective immunosuppressive agents, transplant medicine now has to face the challenge of direct and indirect consequences of lifelong impaired immunity. All disciplines in medicine are invited to contribute their knowledge, innovation, and strategies to aid transplant medicine in the rewarding struggle against malignancies in organ transplant recipients.

Peter Neuhaus

Acknowledgements

The management of skin cancer in organ transplant recipients is an evolving medical speciality, influenced by intensive clinical and basic research efforts in recent years, and inspired by the escalating burden of transplant-associated skin malignancies.

This monograph shall serve as an effective resource for an interdisciplinary readership and aspires to translate insights from basic skin cancer research into the practical steps in skin cancer prevention, diagnosis, and management as it specifically relates to organ transplant recipients. New diagnostic and therapeutic standards are included and commented on. Separate chapters have been devoted to skin cancer prevention and to the essential role of clinical studies in providing an evidence base and in improving treatment outcome.

The clinician will find interdisciplinary, personal experiences together with new concepts for his daily interaction with organ transplant patients.

We are indebted to our co-editors: Sylvie Euvrard, Charlotte Proby, Jan-Nico Bouwes Bavinck, Ed Geissler, Paul Harden and Jaques Dantal for their excellent cooperation and endeavour in producing this monograph. We are indebted to Petter Gjersvik for his invaluable editorial advice and skilful contribution to many of the topics presented herein.

The editors would like to thank all authors for their outstanding contributions to this monograph and for their interest and endeavour in the field of transplant oncology.

The publication of this monograph would not have been possible without the dedication, hard work and enthusiasm of the project coordinator, Birgit Hinrichs.

The skin cancer burden in organ transplant recipients is a growing challenge for us all.

Berlin, Germany

Eggert Stockfleth
Claas Ulrich

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Contributors

Mauro Alaibac, MD, PhD Unit of Dermatology, University of Padova, Via C. Battisti 206, Padova, Italy

Nicole Basset-Seguin, MD, PhD Department of Dermatology, Hôpital Saint-Louis, Policlinique de dermatologie, 1 avenue C Vellefaux, Paris, France

Stefan Beissert, MD Department of Dermatology, University Hospital Muenster, Von-Esmarch-Str. 58, 48149 Muenster, Germany

Anna Belloni Fortina, MD Unit of Dermatology, University of Padova, Via C. Battisti 206, Padova, Italy

Jan D. Bos, MD, PhD, FRCP Department of Dermatology, Academic Medical Center, University of Amsterdam, 1100 DE Amsterdam, The Netherlands

Jan N. Bouwes Bavinck, MD, PhD Department of Dermatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

José M. Carrascosa, MD Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

Delphine Casabonne, MSc Cancer Epidemiology Unit, Richard Doll Building, University of Oxford, Oxford, OX3 7LF, United Kingdom

Rino Cerio, BSc, FRCPath, FRCP (Lond.), FRCP (Edin.), DipRCPath Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry; Departments of Dermatology and Pathology, Barts and The London NHS Trust, London, United Kingdom

Alvin H. Chong, MBBS, MMed, FACD Department of Medicine (Dermatology), St. Vincent's Hospital Melbourne and Skin and Cancer Foundation Victoria, The University of Melbourne, Victoria, Australia

Alain Claudy, MD Department of Dermatology, Hôpital Edouard Herriot, 69437 Lyon, Cedex 03, France

Jacques Dantal, MD, PhD Department of Nephrology and Clinical Immunology, University Hospital Hôtel Dieu, 30 Bd Jean Monnet, 44093 Nantes, France

Vincent Donckier, MD Erasme Hospital, Free University of Brussels, Medicosurgical Unit of Liver Transplantation, Lennik Road 808, 1070 Brussels, Belgium

Arucha L. Ekeowa-Anderson, MRCP The Royal London Hospital, Whitechapel, London E1 1BB, United Kingdom

Sylvie Euvrard, MD Department of Dermatology, Hôpital Edouard Herriot, 69437 Lyon, Cedex 03, France

Jason Fallon, MRCPI Department of Dermatology, Beaumont Hospital, Dublin, Ireland

Mariet C.W. Feltkamp, MD, PhD Department of Medical Microbiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

Carlos Ferrándiz, MD Department of Dermatology, Hospital Universitario Germans Trias i Pujol, Badalona, Spain; Universidad Autónoma of Barcelona, Barcelona, Spain

Lara Ferrándiz, MD Department of Dermatology, Hospital Universitario Virgen Macarena, Universidad of Sevilla, Sevilla, Spain

Peter Foley, BMedSc, MBBS, MD, FACD Department of Medicine (Dermatology), The University of Melbourne, St. Vincent's Hospital Melbourne, Melbourne, Australia

Camille Frances, MD Department of Dermatology, APHP Hospital Tenon Paris, Paris, France

Maria J. Fuente, MD Department of Dermatology, Hospital Universitario Germans Trias I Pujol, Badalona, Barcelona, Spain

Edward K. Geissler, PhD Department of Surgery, University Hospital Regensburg, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany

Alexandra Geusau, MD Division of Immunology, Department of Dermatology, Allergy and Infectious Diseases, Medical University of Vienna, Vienna, Austria

Karen L. Gibbon, FRCP Barts and the London NHS Trust, London, E1 1BB, United Kingdom

Petter Gjersvik, MD, PhD Department of Dermatology, University of Oslo, Rikshospitalet, N-0027 Oslo, Norway

Bernard Grandchamp, MD, PhD Department de Biochemie Hormonale et Génétique, Hôpital Bichat, Paris, France

Adèle C. Green, MBBS, PhD Queensland Institute of Medical Research, Brisbane, Queensland 4029, Australia

Frank R. de Gruijl, PhD Department of Dermatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

Catherine A. Harwood, BA, PhD, FRCP Center for Cutaneous Research, Institute of Cell and Molecular Science, Barts and The London, School of Medicine and Dentistry, Queen Mary University of London, London; Department of Dermatology, Barts and the London NHS Trust, London E1 2AT, United Kingdom

Günther F.L. Hofbauer, MD Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, 8091 Zurich, Switzerland

Beata Imko-Walczuk, MD Clinical Department of Plastic Surgery and Burns Treatment, Medical Academy of Gdansk ul., ul. Debinki 7, 80-952 Gdansk, Poland

Jean Kanitakis, MD Department of Dermatology, Edouard Herriot Hospital, 60437 Lyon Cedex 03, France

Peter Karran, PhD Cancer Research UK, London Research Institute, Clare Hall Laboratories, South Mimms, United Kingdom

Georgios Katsanos, MD Erasme Hospital, Free University of Brussels, Medicosurgical Unit of Liver Transplantation, Lennik Road 808, 1070 Brussels, Belgium

Celeste Lebbé, MD, PhD Department of Dermatology, APHP Hospital Saint Louis, Paris Inserm U 716, France

Irene Leigh, OBE, MD, DSc (Med), FRCP, FMedSci College of Medicine, Dentistry and Nursing, University of Dundee, Ninewells Hospital & Medical School, Dundee DD1 9YS, United Kingdom

Rosalie M. Luiten, PhD Department of Dermatology, Netherlands Institute for Pigment Disorders, Academic Medical Center, University of Amsterdam, 1005 AZ Amsterdam, The Netherlands

Robin Marks, MBBS, MPH, FRACP, FACD Department of Dermatology, University of Melbourne, Melbourne, Australia

Emmanuel Mahé, MD Department of Dermatology, Ambroise Paré University Hospital, Assistance Publique- Hôpitaux de Paris, Boulogne-Billancourt, France

Jane M. McGregor, MA, MD, FRCP Center for Cutaneous Research, Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, London E1 2AT, United Kingdom

Thomas Meyer, PhD Institute of Medical Microbiology Virology and Hygiene, University Hospital Hamburg-Eppendorf, University of Hamburg, Martinistrasse 52, Hamburg, Germany

Emmanuel Morelon, MD, PhD Département de Transplantation, Université Claude-Bernard Lyon 1, Hôpital Edouard Herriot, Pavillon P, Lyon, France

Gillian M. Murphy, MD, FRCPI, FRCP (Edin) Department of Dermatology, Beaumont and Mater Misericordiae Hospitals and Royal College of Surgeons in Ireland, Dublin, Ireland

Luigi Naldi, MD Centro Studi GISED, Department of Dermatology, Ospedali Riuniti, 24100 Bergamo, Italy

Peter Neuhaus, MD, PhD Department of General and Transplantation Surgery, Charité – Universitätsmedizin Berlin, Campus Virchow, 13353 Berlin, Germany

Jonathan Ng, BMedSc, MBBS Department of Dermatology, St. Vincent's Hospital Melbourne, Skin and Cancer Foundation, Victoria, Australia

Steve Nicholson, PhD, MRCP University Hospitals of Leicester, Leicester, UK

Ingo Nindl, PhD DKFZ – Charité Cooperation, Viral Skin Carcinogenesis, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 242, 69120 Heidelberg, Germany

Clark C. Otley, MD Mayo Clinic College of Medicine, Chair, Division of Dermatologic Surgery, Department of Dermatology, Mayo Clinic, Rochester, MN, USA

Conal M. Perrett, PhD, MRCP Center for Cutaneous Research, Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London

Andrea Peserico, MD Unit of Dermatology, Univesity of Padova, Via C. Battisti 206, Padova, Italy

Herbert Pfister, PhD Institute of Virology, University Hospital Cologne, Fürst-Pückler-Straße 56, 50935 Cologne, Germany

Stefano Piaserico, MD, PhD Unit of Dermatology, University of Padova, Via C. Battisti 206, Padova, Italy

Elsemieke I. Plasmeijer, MD Department of Medical Microbiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

Erich Pohanka, MD Division of Nephrology and Dialysis, Internal Medicine III, Medical University of Vienna, Vienna, Austria

Charlotte M. Proby, FRCP Division of Surgery and Oncology, College of Medicine, Dentistry and Nursing, University of Dundee, Ninewells Hospital, Dundee, DD1 9SY, United Kingdom

Henry W. Randle, MD, PhD Department of Dermatology, Mayo Clinic College of Medicine, Jacksonville, FL, USA

Frank Rösl, PhD Division Viral Transformation Mechanism, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 242, 69120 Heidelberg, Germany

Fabrizia Sassi, MD Centro Studi GISED, Ospedali Riuniti, Bergamo, Italy

Thomas Schwarz, MD Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Schittenhelmstraße 7, 24105 Kiel, Germany

Deniz Seçkin, MD Department of Dermatology, Faculty of Medicine, Başkent University, 5. sokak No. 48, Bahçelievler, 06490, Ankara, Turkey

Stephen Shumack, MBBS, FACD The St. George Dermatology and Skin Cancer Center, Kogarah, Sydney, Australia

Mark Simmonds, PhD Cancer Research UK Skin Tumour Laboratory Institute of Cell and Molecular Science, 4 Newark Street, London E1 2AT, United Kingdom

Nadem Soufir, MD, PhD Department of Dermatology, Laboratoire de Biochimie Hormonale et Génétique, IFR02, Hopital Bichat-Claude Bernard, 46 rue Henri Huchard, Paris, France

Eggert Stockfleth, MD, PhD Skin Cancer Center Charité, Department of Dermatology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

Alan Storey, BSc, PhD Molecular Oncology Department, Weatherall Institute for Molecular Medicine, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom

Linda Struijk, PhD DDL Diagnostic Laboratory, Fonteynenburghlaan 5, 2275 CX Voorburg, The Netherlands

Jean-Louis Touraine, MD Département de Transplantation, Université Claude-Bernard Lyon 1, Hôpital Edouard Herriot, Pavillon P, Lyon, France

Richard Turner, MBBS, FRCP Department of Dermatology, The Churchill, Headington, Oxford, OX3 7LJ, United Kingdom

Claas Ulrich, MD Department of Dermatology, Transplant-Aftercare Unit, Charité – Universitätsmedizin Berlin, 13353 Berlin, Germany

Pieter Voskamp, MSc Department of Dermatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

Hermina C. Wisgerhof, MD Department of Dermatology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands

Fenella Wojnarowska, MD Department of Dermatology, Radcliff Hospital, University of Oxford, Oxford, OX3 7LJ, United Kingdom

Introduction – Historical Perspective

Georgios Katsanos and Vincent Donckier

"She was of divine race, not of men, in the fore part a lion, in the hinder a serpent, and in the middle a goat, breathing forth in terrible manner the force of blazing fire. . . ." This description by Homer of the mythical creature called Chimera is one of the first known bibliographic references supporting the idea of beings made out of several creatures joined together in a single one. The concept of combining parts of different bodies into one functioning entity is a very old one, expressed mainly in the forms of myths and incarnated via fearsome monsters (chimera), seductive legends (mermaids), luring nymphs (sirens), and many more.

This fictional concept started to materialize initially by the work of an Indian surgeon, Sushruta (1000 BC), who developed a technique to reconstruct large nasal defects by skin grafts, a technique still used in modern plastic surgery. Sushruta was the first surgeon ever recorded to perform transplantation with homologue tissue transfer in the form of skin grafts.

Tissue restoration is found again in the literature in 15 A.D. in the form of a miracle. St. Agatha was sentenced to "be bound to a pillar and her breasts be torn off with iron shears." She endured this prolonged and horrific torture, and she was left in a dungeon to die, only to be visited by St. Peter, who restored her breasts.

The first reference to organ transplantation for therapeutic purposes comes from China, where Hua-To (136–208 A.D.) allegedly replaced diseased organs with healthy ones in patients under analgesia. In the year 300 A.D., Cosmas and Damian performed the miracle of grafting a cadaveric limb onto a person with a diseased leg, marking the first reference to cadaveric grafts. In 1200 A.D., St. Anthony of Padua reported grafting the foot of a young man who had deliberately mutilated himself. All these references depict the development of the concept of organ and tissue transplantation and its evolution from myth, legend, and rumor through the centuries.

The voyage from fiction and myth to reality proved to be a long one, as the dark ages cast a thick shadow upon all scientific development. In the 16th century, the Italian surgeon Gasparo Tagliacozi revived the ancient Indian method of nose

G. Katsanos (✉)
Medicosurgical Unit of Liver Transplantation, Erasme Hospital, Free University of Brussels, Brussels, Belgium

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reconstruction and further developed it by using skin grafts from the inner arm in a two-stage reconstruction. The 17th century is marked by the work of John Hunter, an extraordinary experimental surgeon from Scotland who worked with autografts. One of his famous experiments was the autotransplantation of a cock's claw to his comb.

In 1901, Karl Landsteiner, an Austrian physician, described the first three human blood groups, A, B, and O, and 1 year later, Decastrello and Sturli found the fourth blood type, AB. Landsteiner received the Nobel Prize for his work in 1930. By 1907 blood transfusion became safe, as Reuben Ottenberg performed the first blood transfusion using blood typing and cross-matching.

In the beginning of the 20th century, a famous figure of surgery appeared in the literature, named Alexis Carrel. Born in Lyon in 1873 and trained in France, this skilled experimental surgeon wrote in 1906: "The question of the transplantation of organs in man is a very serious one and difficult, for will the transplanted organ remain and function normally for a long period of time? Another difficulty would be that of finding organs suitable for transplantation into man. A process of immunization would no doubt be necessary before the organs of animals would be suitable for transplantation into man. Organs from a person killed by accident would no doubt be suitable." Carrel described a technique of effective vascular terminoterminal anastomosis, resolving some major technical difficulties of organ transplantation such as graft thrombosis, opening thus the gates for the realization of organ grafting.

This technical advance marks the beginning of a new era in transplantation, the era of multidisciplinary medicine. Surgeons soon realized that overcoming technical difficulties of surgical practice was just the beginning of a difficult journey as immunological issues began to emerge. Remarkably also, in 1910 Carrel intuitively described the problem of graft rejection: ". . .the changes undergone by the organ would be due to the influence of the host, that is, biological factors." From there on, biology, medicine and surgery would have to advance side by side in order to achieve the miracle of transplantation in the form we know it today.

In 1914, Murphy observed that rejected organs are infiltrated by lymphocytes, and with subsequent experimental studies he showed that lymphocytopenia inhibits rejection. Murphy was one of the first researchers to implicate the role of cellular immunity in the rejection process.

In the beginning of World War II, a British medical researcher named Peter Medawar, intrigued by the treatment of burned aviators, focused his research on their treatment with skin grafts. Essentially, when comparing the fate of skin graft taken from the patient itself (autograft) or from another person – the donor – (allograft), Medawar clearly identified the phenomenon of rejection and paved the way for a comprehensive approach to transplantation immunity. By extending his curiosity to animal models, Medawar later demonstrated in mice that full acceptance of foreign skin graft (allograft) could be actively induced by neonatal injection of hematopoietic cells from the donor strain. These pioneer works build the fundamental grounds for the concept of self- and non-self immune recognition and subsequently, for the definition of transplantation tolerance. In the same period, Australian Frank Macfarlane Burnet published his conclusions on immune tolerance and rejection. Medawar and Burnet shared the Nobel Prize for their work in 1960.

The foundations of modern immunology having been laid, the necessity of immunosuppression became evident. The first method of immunosuppression was total body irradiation, characterized by Murray as "blunt and unpredictable." In 1962, the discovery of azathioprine by Nobel Prize laureates Gertrude Elion and George Hitchings and then the discovery of cyclosporine 10 years later, in 1972, by the Swiss biochemist Jean-François Borel, marked the beginning of a new saga, that of organ replacement.

The first organ to be successfully transplanted was the kidney. In 1954, Murray successfully performed kidney transplantation between two monozygotic twins with excellent results. In 1958 Murray, in Boston, and Hamburger, in Paris, started performing a series of human kidney transplantations, initially using total body irradiation as immunosuppression and later the available immunosuppressive drugs.

The success of kidney transplantation sparked the hopes of replacing other organs, and in 1966 W.D. Kelly performed the first human, whole-organ pancreatic transplantation for treatment of type 1 diabetes mellitus. However, this important breakthrough was marked initially by poor results, and very few pancreatic transplantations were performed until 1978, when the combination of newer immunosuppressive drugs and innovative surgical methods yielded acceptable results.

The first human lung transplantation was performed by D. Hardy and his colleagues at the University of Mississippi Medical Center in 1963. The 58-year-old patient died 8 days after the operation of renal complications. Seven years later, Belgian doctors of the University of Ghent performed a successful pulmonary transplantation in a patient with end-stage lung disease. Their patient survived for 10 months.

In 1963, Thomas Startzl performed the first orthotopic liver transplantation. Initial results were disappointing, but Startzl's perseverance and extraordinary surgical skills prevailed, and liver transplantation became a reality. In 1967 Christian Barnard performed a cardiac transplantation in a 54-year-old patient. The operation was successful, and the transplanted heart functioned for 18 days, when the patient succumbed to pneumonia.

Although small bowel transplantation was first performed before 1970, the ubiquitous rejection and total graft failure at the time discouraged the surgical community. However, with the cyclosporine revolution the interest in small bowel grafting was revived and along with the modern immunosuppressive agents, the first successful small bowel transplantation with long-term survival was performed in Germany in 1988 with a graft survival of 4 years.

An important date is the year 1967, when Jan van Rood founded Eurotransplant in an effort to coordinate and optimize organ allocation. The model of Eurotransplant is to establish a central registration of patients on waiting lists and then organize transparently the organ allocation according to equitable medical criteria.

Somehow victims of their success, transplant programs rapidly evolved, and new medical and ethical problems emerged, such as organ shortage, the need to define donor legislation, and priority criteria. In 1984, the National Organ Transplant Act in the United Kingdom laid solid foundations in the medico-legal aspect of human transplantation, setting an elaborate frame for further development in this field by

establishing the Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Yet, major concerns remain concerning illegal or unethical activities, such as organ trafficking or transplant tourism.

After a long voyage through the centuries and with the contribution of great minds, organ transplantation is now a reality in every day medical practice. In multidisciplinary coordinated efforts, involving surgeons, physicians, anesthesiologists, immunologists, and researchers across the world, many obstacles have been tackled. Later advancements have come from the technical side, such as the development of living donor transplantations, but also from the pharmalogical side, including the discovery of tacrolimus in 1990, daclizumab in 1997, and sirolimus in 1999. Major challenges have still to be faced, notably, the long-term toxicity of immunosuppressive agents and the problem of organ shortage. These are the key points to improve long-term quality of life of transplant recipients but also to reduce the mortality while waiting for transplantation. As a matter of fact, chronic immunosuppression now represents the leading cause of morbidity and mortality after organ transplantation. Many efforts are currently being made to design new therapeutic strategies, aiming at reducing or discontinuing post-transplant immunosuppression, establishing the so-called transplantation tolerance. In parallel, great hopes are also generated by stem cell researchers as an alternative to whole organ transplantation. Scientists at the University of Minnesota managed to create a functioning rat's heart from the animal's stem cells in the beginning of 2008, opening a door to custom organ creation from the recipient's cells, alleviating any need for immunosuppression.

The future of transplantation is colorfully depicted by the quote of Dr. Doris Taylor of the University of Minnesota: "...What we've done, is hopefully open a door to the idea that we can actually begin to build not just pieces of tissue and organs, but build organs...our hope is that if you need it, we can make it."

Skin Cancer After Transplantation: Where Did We Come From, Where Do We Go?

Robin Marks

When Paul Gerson Unna first described a possible relationship between sunlight and development of cutaneous epithelioma, he would have had no idea of the impending public health epidemic of these tumours to be seen in the 100 years following his publication.

The incidence of sun-related skin tumours, including melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), has been increasing in virtually every fair-skinned population in which they have been studied throughout the world. Nonmelanoma skin cancers (SCC and BCC) are now the most common cancers in Australia, occurring at least three times more commonly than all other cancers combined. By virtue of their number, they now comprise the biggest burden of all cancers to the health budget in Australia. Variations on this exist in many other countries where there are fair-skinned populations exposing large amounts of their skin to hot sunny climates. In Australia, the latest data suggest that at least two of three people born in the country will eventually develop one of the nonmelanoma skin cancers (NMSCs).

There has been increasing awareness of the public health implications of skin cancer, as was initially reported in the incidence data. The mortality from NMSC has been traditionally very low, with the majority being from SCC. Many organisations have started public health programs on prevention and early detection of skin cancer. Much research is being done into the basic pathogenesis of these tumours, and our knowledge has expanded enormously. There is also much work being done on new forms of treatment, particularly topical treatments, which will gradually replace surgery over time.

In the public health area there have been some remarkable changes in knowledge, attitudes, and behaviours in the sunlight in some countries, Australia in particular. There are early data suggesting a reversal in the increasing incidence and mortality caused by melanoma in younger cohorts in Australia and a similar change in incidence of BCC. But does this mean that we can sit back and relax with the reassurance that it will all be over soon? Of course the answer is no. There is a "new kid

R. Marks (✉)
Department of Dermatology, University of Melbourne, Melbourne, Australia

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on the block" – organ transplantation – and this has brought a new dimension to the epidemic of skin cancer.

Whether or not people develop a skin cancer is a combination of their genetic susceptibility and the circumstances in which they have lived their life. Even if they do achieve the right combination to initiate the cellular changes in keratinocytes that we recognise as dysplasia, a variety of mechanisms will act to control further tumour development, immunological mechanisms in particular. A reduction in, or a lack of, these immunological control mechanisms will inevitably lead to an increased ease of induction of what we recognise as invasive cancer. And that is exactly what is being found in patients who have undergone organ transplantation. The immunological surveillance and control currently reduced to prevent transplant rejection is the same as that preventing tumour formation. Thus, predictably, successful organ transplantation is followed by an increased risk of skin cancer, particularly SCC.

Following organ transplantation, it is not just the formation of one or two tumours that is the concern. Very large numbers of tumours, SCCs in particular, develop over time in those at risk. It creates an enormous challenge to everyone involved, both patients and those responsible for their care. So where do we go from here? What can be done?

There are different approaches to disease control. The first and perhaps the most ideal would be to reduce an individual's genetic susceptibility to develop the disease, in this case skin cancer. Ironically, at the moment this is the most difficult of the approaches, as it is the area in which we have the least knowledge and the least ability to bring about the changes necessary.

Another problem with this simplistic-sounding approach is that by the time many people require their organ transplantation, they have often gone a long way along the pathway that leads to tumour formation. This means, for example, that they may have actinic keratoses already and thus reducing genetic susceptibility would occur too late.

Another approach might be to develop more targeted, or more specific, immunosuppression. Ideally, this would reduce the risk of transplant rejection but would not reduce tumour rejection. There is a promise of this with, for instance, the mTOR inhibitors, but a long-term benefit in skin cancer reduction is not yet proven and must be balanced against other, possibly less favourable, drug characteristics.

The public health approach to skin cancer control would comprise the two classical components. The first component is to deal with the problem people have now, that is, incipient or overt tumours. These must be detected early, either in the "precancerous" stage, or very early in the truly invasive phase, thus allowing an easy cure to be achieved with relatively simple treatment.

The second component of a public health approach is the long-term goal of trying to prevent skin cancer: This is to reduce environmental exposure to the carcinogen that precipitates the tumours in susceptible people: sunlight. The ideal here is to commence photoprotection at a very early pretransplant stage and to continue it to an almost obsessional degree post transplant. Complications of excessive photoprotection, such as vitamin D deficiency, could be easily overcome through dietary vitamin D supplementation.

The final approach is the “when all else fails-approach.” There is the need for better skin cancer treatments that are effective, simple, ideally applied by the patient themselves, and that are not too expensive. As transplant patients frequently have diffuse sun-related changes in their skin, it is necessary to take a broader view of the therapeutic approach. Some people have termed this “treating the field” rather than just treating individual tumours if or when they become clinically apparent.

So, in summary, the need for a book such as this one is a clear indication that the development of skin cancer in patients undergoing organ transplantation is not just a problem now. It also will be an increasing problem in the future, as an increasing number of people are treated with this therapeutic approach to organ failure.

There is no doubt that there have been very many advances over the years in all the components underpinning successful organ transplantation. It is to be hoped that, by exploring all or many of the possibilities to deal with skin cancer outlined here, this side effect of organ transplantation will become less of a problem in the future.

Part I
Transplant Medicine

De Novo Post-Transplantation Malignancies: Incidence and Risk Factors

Jacques Dantal

Introduction

An increased incidence of cancer in immunodeficient and immunosuppressed patients is now well established. Improvements in transplantation procedures and immunosuppressive therapies have resulted in better short-term and long-term graft survival, but immunosuppression exposes patients to long-term complications [1]. Malignancies are becoming the greatest limiting factor for patient and graft survival following kidney transplantation, even as incidence of death related to cardiovascular diseases and infections is decreasing [2]. Cancers are frequently more aggressive in transplant patients and are more likely to be fatal than would be expected in patients who have not undergone transplantation [3].

The majority of information concerning cancer in transplant patients comes from registries such as the CTTR (Cincinnati Transplant Tumor Registry), created by Penn in 1970 [4], or the ANTR (Australian and New Zealand Transplant Registry [5] in the case of kidney transplantation, and from many single-center [6–9] or regional [10–12] registries studies. Nevertheless, the majority of studies reporting on the incidence and risk factors for de novo cancers post transplantation have used different control populations and methodologies and have focused on the most frequent type of tumors, which are virus-related cancers such as nonmelanoma skin cancers.

Overall Incidence of De Novo Cancer After Organ Transplantation

It is clear that de novo post-transplantation malignancies are a problem shared by all transplant patients regardless of the organ that has been transplanted.

J. Dantal (✉)
Department of Nephrology and Clinical Immunology, University Hospital Hôtel Dieu, 30 Bd Jean Monnet, 44093 Nantes, France

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Kidney Transplantation

The global reported cancer incidence in renal transplant recipients ranges from 2.3% to 31%, depending on the report in question (for review, see reference [13]). This large variation is mainly caused by differences in the length of follow-up. In fact, the incidence is clearly underestimated in some reports because of the lack of long-term follow-up and the absence of systematic detection of cancer, especially cancers affecting the skin. For example, a maximum cumulative incidence above 75% and 33% has been observed in patients followed for more than 30 years, for skin and non-skin cancers, respectively [14]. Nevertheless, a precise assessment of cancer incidence is difficult in the context of small cohorts or single-center studies, and cancer incidence must not be calculated as a global percentage that is biased by the large group of recently transplanted patients.

More informative results from two large studies were reported recently. Kasiske et al. compared the incidence of cancers by linking the data from the United States Renal Data System (USRDS) and the Medicare billing claims for cancer [15]. This study was performed over a 3-year follow-up period, among three large populations (more than 35,000 transplant patients, the general population, and patients awaiting a kidney transplantation) between 1995 and 2001. In transplant recipients, the cumulative incidence of nonmelanoma skin cancer (NMSC) and non-skin cancer (but including melanoma and Kaposi's sarcoma, KS) was 7.43% and 7.45%, respectively. Compared to the general population, the risk of cancer was increased for all types of tumors, but when compared to the waiting list patients, an increased risk of cancer emerged for only some types, mainly virus-related cancers (NMSC, KS, and non-Hodgkin's lymphoma).

The second study, involving more than 28,500 Australian renal transplant recipients and linking data from ANTR and the Australian National Cancer Statistics Clearing House, found similar results [16]. The overall incidence of cancer, excluding NMSC and those known to be related to end-stage renal disease, was clearly increased after transplantation [standardized incidence ratio (SIR): 3.27; 95% confidence interval (CI): 3.09–3.46]. Compared to the general population, the risk of cancer was slightly increased during end-stage renal failure and dialysis (SIR: 1.16; CI 1.08–1.25; and SIR: 1.35; CI: 1.27–1.45, respectively). In addition, most cancers with a risk in excess of 3 were suspected to be of viral origin (see below).

Heart and Lung Transplantation

The Registry of the International Society for Heart and Lung Transplantation showed that 3.1%, 16.1%, and 26.2% of heart transplant recipients presented malignancies after 1, 5, and 8 years of follow-up, respectively [16], and 4%, 18%, and 30% of lung transplant recipients presented malignancies after 1, 7, and 9 years, respectively. The authors suggested that the risk of developing NMSC was greater in heart than in kidney transplant patients [17], but that subsequent recurrence of

NMSC was more frequent in kidney recipients [18]. The results from the Collaborative Transplant Study (CTS) demonstrated that, relative to the general population, the risk of non-Hodgkin's lymphoma was highly increased in lung as well as in heart transplant recipients compared to recipients of kidneys from deceased donors (5-year relative risk at 239 and 58.6 compared to 12.3) [19].

Liver Transplantation

An increased incidence of de novo cancer has also been reported after liver transplantation. However, very few studies have assessed the extent of the increased risk compared to the general population. One recent study reported the observed cancer incidence in a cohort of 1,778 patients transplanted in England and Wales between 1982 and 2004, compared to a matched control group [20]. In this publication, 7.9% of all patients developed some form of cancer (median follow-up of 65 months) and had an increased incidence for all types of tumors (SIR: 2.07; CI: 1.74–2.44). Another study, in the United States, reported a 3.16-fold increase in cancer incidence (skin carcinoma excluded from the analysis) in patients surviving for more than 5 years after liver transplantation compared to the general population [21]. Finally, the cumulative incidence of de novo cancer at 5, 10, and 15 years after liver transplantation was 2%, 6%, and 15%, respectively [22], apparently lower than that reported for other types of organ transplantation.

Type of Malignancy

Once the post-transplant cancer incidence has been established, it is crucial to ascertain the distribution pattern of the different types of neoplasia. In the CTTR, 40% of the tumors registered affected the skin, 11% were lymphoproliferative disorders, 4% were KS, 4% affected the cervix and kidney, and 3% were vulva and perineum cancers [23, 24]. Although all types of malignancies were reported in the transplant population, a specific pattern could be distinguished in these immunosuppressed patients. Compared to the general population, cancer distribution in patients from the CTTR registry showed an increase from 6% to 24% for lymphomas, from almost 0% to 4% for KS, from 2% to 5% for kidney cancer, and from 0.7% to 3% for vulva cancer. A similar pattern of distribution was reported for all the registries [25, 26].

Perhaps the most interesting analyses come from large cohort studies of transplant patients in comparison with matched control populations (the general population or patients awaiting transplantation or under dialysis). These studies enable calculation of the risk ratio (RR) or standardized incidence ratio (SIR). In the USRDS/Medicare analysis concerning renal transplant recipients [15], the incidence of common cancers, such as those of the breast, prostate, lung, or colon, was roughly 2-fold higher than that observed in the general population after 3 years of

follow-up. Nevertheless, when compared to patients on the transplant waiting list, the incidence of most malignancies was similar, with the exception of KS (9-fold increase), non-Hodgkin's lymphoma (3.3-fold increase), NMSC (2.6-fold increase), and melanoma and cancer of the mouth (2.2-fold increase in both cases). Renal carcinomas were also increased (by 39%) as well as leukemia and esophageal cancers. Finally, prostate and ovarian cancers were less frequently observed after renal transplantation than during the period on the waiting list.

The major shortcomings of this study are a short duration of follow-up (3 years) and a possible bias in the population studied, not reflecting the whole transplant population, but rather patients who have Medicare as their primary provider (47% of the whole population). In another study, an increased incidence of only a few types of cancer was reported before renal replacement therapy and for some patients during dialysis, whereas an increased incidence of a wide range of types was observed after kidney transplantation [29]. The cancers that were found to have an increased incidence during end-stage renal disease, but before dialysis, were limited in type, including non-Hodgkin's lymphoma and KS, suggesting some degree of immune deficit resulting from renal failure or a role of the immunosuppressive medication given to treat certain renal diseases.

Some publications concerning the dialysis period reported no [27] or only a slightly increased [28] cancer risk. In a large international collaborative study, after a mean follow-up of 2.5 years, the cancer incidence was found to be increased in patients undergoing dialysis, especially for cancers of the kidney (RR: 3.6; CI: 3.45–3.76), bladder (RR: 1.5; CI: 1.42–1.57), and thyroid and other endocrine glands (RR: 2.28; CI: 2.03–2.54) [28]. Among the cancers found to have an increased incidence in dialysis patients, those of viral etiology were very common (KS, liver, cervix, tongue) [29]. In addition, the risk of cancer was particularly high in young dialysis patients (less than 35 years of age; RR: 3.68; CI: 3.39–3.99).

After transplantation, no cancers have been reported as having a lower incidence than that observed in the general population. A risk similar to the general population has been frequently observed for the more common cancers such as prostate and breast cancer [29]. In contrast, an increased incidence of prostate cancer (SIR: 3.6; CI: 1.55–7.06) was observed in a French cohort of renal transplant recipients in comparison to the age-matched general population [30].

It has been clearly demonstrated that, after transplantation, cancers known or suspected to be related to viral agents are the most representative types [29]. Among the 18 types of cancer with a relative risk above 3, more than 50% are related to viral infection: KS caused by human herpesvirus 8, non-Hodgkin's lymphoma, and Hodgkin's disease related to Epstein–Barr virus, liver cancer related to hepatitis B or C, and the large group of cancers related to human papilloma virus (NMSC, tongue, mouth, vulva, vagina, and penis). For some other frequent localizations, the evidence for human papilloma virus involvement is limited or inconclusive (nasal cavity, esophagus, eye, salivary gland), and only for a few remaining localizations is the association with a viral infection not actually suspected. In addition, other cancers related to human papilloma virus infection were also significantly increased with a relative risk below 3 (cervical and anal cancers), lending credence to a pivotal

role for viral infection in the development of cancer in immunosuppressed transplant recipients.

The incidence of cancers known to be associated or at the origin of end-stage renal failure, such as urothelial and kidney cancers or myeloma, was increased for all the periods studied (before dialysis, during dialysis, and after transplantation). Finally, analysis of these three periods of renal disease revealed that preexisting personal factors and/or end-stage renal failure or the dialysis procedure itself were not involved in the increased cancer incidence observed after kidney transplantation.

Although the incidence of NMSC, KS, and lymphoproliferative disorders was also increased regardless of the type of transplantation, the incidence of some other types of cancer, such as those related to organ-specific diseases, could also be increased after immunosuppression. After heart transplantation, the incidence of bronchogenic carcinoma remains controversial. Some authors have reported an incidence similar to that observed in the general population [31]. Lung cancer is one of the most common causes of cancer-related deaths in the United States. Accordingly, lung cancer in transplant patients would be expected to occur on the basis of chance alone. Nevertheless, other authors have reported an increased incidence of lung cancer in transplant patients [32]. This type of cancer occurred in 0.28% to 4.1% of heart and lung transplant recipients, and the risk was approximately 20 to 25 times that of the general population [33, 34]. In addition, one study reported an increased incidence of primary lung cancer after single lung transplantation compared to a matched population of bilateral lung recipients with comparable native disease, age, and tobacco history [34]. However, these cancers were frequently diagnosed after systematic X-ray examination whereas chest CT screening is recommended in high-risk patients (>10 pack/year smoking history) [35].

In some publications, colon and oropharyngeal cancers are reported as having a high overall incidence subsequent to liver transplantation. Colon carcinoma represents 3% to 14% of all tumors observed with an incidence of less than 1% in most of the series reported, but the relative risk could be as high as 12.5 times that observed in the general population [22]. In the liver transplant population, this cancer could be related to the initial hepatic disease (i.e., primary sclerosing cholangitis), which is frequently associated with inflammatory bowel disease, especially ulcerative colitis. Although this subgroup of patients is at a high risk of developing colorectal carcinoma [36], the incidence of colic carcinoma is not increased in all studies of transplant recipients [37]. Oropharyngeal cancers presented an incidence ranging from 0.2% to 1.5% and represented up to 21.9% of the overall tumors in liver transplant patients [38,39]. These types of tumors are related to alcohol consumption and tobacco history and were only reported in patients requiring transplants for alcoholic liver cirrhosis [40]. When compared to nontransplant patients with similar risk factors, these cancers do not occur more frequently after liver transplantation [41]. Finally, after renal transplantation, hepatocarcinoma is a long-term complication for patients with hepatitis B and/or C infection [42], but after liver transplantation recurrence of viral infection is the main problem, and an increased incidence of de novo cancer is still questionable [43, 44].

Risk Factors for De Novo Cancer After Organ Transplantation

Post-transplant de novo malignancies are the result of complex interactions between immunological and nonimmunological factors. As for the general population, many conventional risk factors, such as age, gender, cigarette smoking, and sun exposure, contribute to the incidence of cancers. Age, which is known to be associated with a decrease in immunosurveillance, is a strong predictor of skin and non-skin malignancies after renal transplantation [12, 45]. In addition, being over the age of 60 is an independent risk factor for non-Hodgkin's lymphoma in transplant patients [45]. Moreover, the overall risk of developing a cancer after transplantation is thought to correlate closely with cumulative exposure to and type of immunosuppressive medication (as described in more depth in the section by E. Geissler in this volume). Finally, there is a strong association with nonimmunological factors such as individual risk factor and environmental exposure in the genesis of cancer for transplant recipients.

All data collected to date from single-center and registry studies indicate that transplant recipients are at risk of developing the types of cancer that have an established or suspected viral etiology [29]. Even when excluding these cancers from the analysis, the risk of cancer remains at least twice that observed in age-matched controls. Certain viral infections are clearly linked to the development of specific types of malignancies. For example, Epstein–Barr virus (EBV) is associated with post-transplantation lymphoproliferative disorders [see reference [46] for review], human herpesvirus 8 is frequently associated with Kaposi's sarcoma [see reference [47] for review], human papilloma virus is associated with a large variety of epithelial cancers (skin, cervix, penis, or anogenital carcinomas) [see reference [48] for review], and hepatitis virus B and C are linked to the development of hepatic cell carcinoma [see reference [49] for review]. All these viruses share the capacity to control cell cycle and division, as well as escape from apoptosis, thus sustaining transformation and cell growth. In addition, proliferating tumor cells can easily escape from T-cell surveillance when this is impaired by the immunosuppressive therapies. As a consequence, intense immunosuppression is the main risk factor for virus-related cancers. Post-transplant lymphoproliferative disorders (PTLD) are more frequently observed after T-cell depletion by antithymocyte globulins [19] or treatment with Orthoclone OKT3 [50], and cancers (mainly skin cancers) are more frequently observed in patients exposed to a high versus low regimen of cyclosporin A [6] or when exposed to a triple drug regimen combining cyclosporine A, azathioprine, and corticosteroids [51]. The role of immunosuppression is described in this book in more detail by P. Harden.

The origin of the initial disease could also influence the incidence of cancer. Patients who have renal failure as a consequence of type 1 diabetes have a relatively lower risk of cancer (RR: 0.11; CI: 0.03–0.47) [45]. Nevertheless, more studies are required to confirm this observation and to put forward possible explanations. Patients with a history of analgesic abuse [52] or use of Chinese herbs [53] are at a high risk of uroepithelial carcinoma. Some rare primary diseases, especially von Hippel–Lindau and Denys–Drash syndrome, are associated with an intrinsically

higher risk of developing Wilms' tumor [54, 55]. For these patients, genetic predisposition plays a role in the occurrence of de novo post-transplantation malignancies, although this hypothesis could be put forward for more common cases where the occurrence of different types of tumors (mainly skin and others cancers) occurred in the same patient [56, 57].

Cigarette smoking is also a well-known risk factor in the general population, and of course the risk of cancer is increased in immunosuppressed organ recipients with concurrent tobacco use [58]. Tobacco has a central role in the etiology of cancers of the lung, head, and neck [59], urinary tract (such as renal cell carcinoma) [60], bladder [61], and pancreas [62], and acts synergistically with alcohol, for oral and esophageal cancers, and probably with human papilloma virus (HPV) infection for some others cancers such as those affecting the cervix [63]. After renal transplantation, patients who smoke more than 25 packs per year at the time of transplantation present a relative cancer risk of 2.26 compared to their non-smoker counterparts (CI 1.51–4.32) [45]. Although active programs against smoking are able to decrease smoking rates, no studies have clearly analyzed the potential effects of smoking cessation before or after organ transplantation. Such analyses are difficult due to the relatively small groups of patients, and it has been suggested that giving up smoking more than 5 years before transplantation does not influence the risk of post-transplantation malignancies [45].

The type and frequency of malignancies vary widely between geographic regions. These differences may be explained by sun exposure, phototype, and prevalence of viral infections. The relationship between sun exposure and skin cancers, which is well established in the general population, also exists in transplant patients. The risk of developing skin carcinoma is extremely high in Australia and in the fair-skinned Caucasoid population [64], while these carcinomas are infrequent in the Asian population [65]. In Japan, the incidence of skin cancer is very low and Kaposi's sarcoma is almost absent. Here the most frequently observed carcinomas are those affecting the digestive organs, which is in accordance with the high incidence of these cancers in this country [66]. In the Chinese population, the distribution pattern of cancer after kidney transplantation was also found to be different from that observed in Western countries; bladder and renal cancers were the most frequent, followed by liver carcinoma (high prevalence of hepatitis B and C in South East Asia), but with no skin cancers [67]. In Saudi Arabia, Kaposi's sarcoma is the most frequent of the malignancies, which can be explained by the high prevalence of human herpesvirus 8 (HHV8) infection [68].

The high prevalence of transplant patients with a history of cancer is a growing problem. A waiting period of at least 2 years and up to 5 years is proposed to avoid any cancer recurrence [69]. This waiting period is not necessary for any types of in situ cancer, basal cell carcinoma, and incidentally discovered renal cancer. The global frequency of recurrence is 21% [70], with highest recurrence rates for breast carcinomas (23%), symptomatic renal carcinomas (27%), sarcomas (29%), bladder carcinomas (29%), nonmelanoma skin cancers (53%), and multiple myeloma (67%). The problem of recurrence is different from that of de novo cancer. It was recently suggested that, in patients suffering from a first cancer before