Desmoid Tumors
Charisse Litchman
Editor

Desmoid Tumors
Preface

Desmoid tumors are currently amongst the rarest of rare tumors that afflict patients. The incidence of these tumors is not as low as is currently believed, however. Misdiagnosed by treating physicians and oncologists alike, especially in cases which remain stable or even regress over time, they may be labeled inaccurately or overlooked entirely. Indeed there are several different pathologic terms for desmoid tumors which confuse the diagnosis. Despite progress in molecular genetic profiling that would aid in precise identification, once designated as benign further efforts at identification are often abandoned.

Over the past decade, at major sarcoma centers, at high esteemed research institutions and at professional meetings such as the prestigious annual CTOS (Connective Tissue Oncology Society) meeting, the importance of understanding desmoid tumors has become increasingly more evident. More research projects were performed and publications submitted in the last 5 years than in the preceding 20 years. Much of this increasing awareness can be credited to the advent of vocal grass-root advocacy groups. Patient education has been heightened through contacts made on-line and powerful alliances forged between researchers, resulting in shared resources and improved outcomes. However, the majority of patients do not receive their care at dedicated sarcoma centers and many oncologists remain unfamiliar with the identification of and currently recommended treatments for desmoid tumors. This book will serve as the first comprehensive publication on the desmoid tumor. Although it may not answer all the questions, as most of these answers have not yet been found, it will introduce the reader, be he a scientist, physician or patient, to what a desmoid is and to the current important players who are leading the guest to find a cure.

Chapter 1 summarizes the increased recognition of the need to identify and treat desmoid tumors; Chap. 2 describes the clinical presentation and epidemiology of desmoid tumors; Chap. 3 discusses the pathology of desmoids; Chap. 4 describes the role of the APC gene and β-catenin in the genesis of desmoid tumors; Chap. 5 reviews the preferred imaging techniques to diagnose and monitor the disease; Chap. 6 outlines the surgical options; Chap. 7 describes current systemic therapy; Chap. 8 and 9 discuss the roles of traditional and interventional radiotherapy in the treatment of desmoid tumors; Chap. 10 describes desmoid tumors in the context of
Familial Adenomatous Polyposis; Chap. 11 addresses the unique features and challenges in treating children and adolescents with desmoid tumor; Chap. 12 details the role of microarrays in studying and distinguishing between desmoids and scar tissue and offers a glimpse into the new techniques of high-throughput sequencing; Chap. 13 outlines the difficulty in categorizing desmoids as benign or malignant and the implications of assigning either label; Chap. 14 examines the role of advocacy groups in promoting better recognition, patient-physician liaisons, researcher interest, desperately needed research funding and emerging patient support systems. Each of these chapters is followed by an extensive list of key references.

I would like to thank all the distinguished authors who enthusiastically agreed to contribute to this book and who without exception are working collaboratively to elucidate the etiology of and advance the search for a cure for this debilitating disorder.

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Charisse D. Litchman, MD
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Contributors

Hani O. Al-Halabi Department of Radiation Oncology, McGill University, Montreal, Canada
e-mail: hani.elhalabi@mail.mcgill.ca

Benjamin Alman Department of Surgery, Division of Orthopedics, The Hospital for Sick Children, University of Toronto, Toronto ON, M5G 1L7. Toronto, Canada
e-mail: benjamin.alman@sickkids.ca

Yen-Lin Chen Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

James Church Department of Colorectal Surgery, Cleveland Clinic Foundation, Cleveland, Ohio 44143, USA
e-mail: church@ccf.org

Chiara Colombo Department of Surgical Oncology and the Sarcoma Research Center, The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
e-mail: ccolombo@mdanderson.org

Anastasia Constantinidou Sarcoma Unit, The Royal Marsden Hospital, London SW3 6JJ, UK
e-mail: anastasia.constantinidou@icr.ac.uk

Thomas F. DeLaney Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA
e-mail: tdelaney@partners.org

Paxton V. Dickson Department of Surgical Oncology, The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
e-mail: PVDickson@mdanderson.org

Joseph P. Erinjeri Department of Interventional Radiology, NYU School of Medicine, New York, NY, USA
e-mail: erinjerj@mskcc.org
Wai Chin Foo  Department of Pathology, The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
  e-mail: wfoo@mdanderson.org

Suzanne George  Department of Medical Oncology, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
  e-mail: suzanne_george@dfci.harvard.edu

Francis J. Hornicek  Department of Orthopaedic Oncology, Massachusetts General Hospital, Boston, MA, USA
  e-mail: fhornicek@partners.org

Sinchun Hwang  Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
  e-mail: hwangs@mskcc.org

Ian Judson  Sarcoma Unit, The Royal Marsden Hospital, London SW3 6JJ, UK
  e-mail: ian.judson@icr.ac.uk

Jonathan Landa  Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
  e-mail: landaj@mskcc.org

Alexander J. Lazar  Departments of Pathology and the Sarcoma Research Center, The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
  e-mail: alazar@mdanderson.org

Robert A. Lefkowitz  Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA
  e-mail: lefkowir@mskcc.org

Dina Lev  Department of Cancer Biology and the Sarcoma Research Center, The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA
  e-mail: dlev@mdanderson.org

Charisse Litchman  Department of Neurology, The Stamford Hospital, Stamford, CT 06904, USA
  e-mail: cdlitchman@gmail.com

Andrea Marrari  Department of Medical Oncology, Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
  e-mail: andrea_marrari@dfci.harvard.edu

Anthony Montag  Departments of Pathology and Surgery, The University of Chicago, Chicago, IL 60637, USA
  e-mail: amontag@bsd.uchicago.edu

John T. Mullen  Department of Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA
Contributors

**Raphael Pollock**  Department of Surgical Oncology, The University of Texas, MD Anderson Cancer Center, Houston, Texas 77030, USA  
e-mail: rpollock@mdanderson.org

**David S. Pryluck**  Department of Interventional Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA  
e-mail: david.pryluck@uphs.upenn.edu

**Matt van de Rijn**  Department of Pathology, Stanford University Hospital and Clinics, Stanford, CA 94305, USA  
e-mail: mrijn@stanford.edu

**Oakleigh Ryan**  Whiton House, Janesville, WI 53545, USA  
e-mail: Oakleigh@whitonhouse.com

**Michelle Scurr**  Sarcoma Unit, The Royal Marsden Hospital, London SW3 6JJ, UK  
e-mail: michellescurr@hotmail.com

**Stephen X. Skapek**  Department of Pediatrics, Section of Hematology/Oncology and Stem Cell Transplantation, The University of Chicago, Chicago, 60637 IL, USA  
e-mail: sskapek@peds.bsd.uchicago.edu

**Robert T. Sweeney**  Department of Pathology, Stanford University Hospital and Clinics, Stanford, CA 94305, USA  
e-mail: sskapek@peds.bsd.uchicago.edu

**Aaron R. Weiss**  Department of Pediatrics, Division of Pediatric Hematology/Oncology, The Cancer Institute of New Jersey, New Brunswick, NJ 08903, USA  
e-mail: weissar@umdnj.edu

**Sam S. Yoon**  Department of Surgical Oncology, Massachusetts General Hospital, Boston, MA, USA
The desmoid tumor (DT) is a rare tumor that arises from connective tissues. The incidence of newly diagnosed tumors is only two to four per one million people per year. The clinical presentation varies depending on its anatomic location and the ensuing devastation can result in limb amputation, bowel obstruction, and even death. The clinical behavior can be just as variable, from locally aggressive with catastrophic potential to stable or even spontaneously regressive disease. The similarity in these nonuniform tumors is their origin in aberrations in the APC/β-catenin pathway, the difficulty in diagnosis, and the lack of well-established protocols for their treatment.

One question that would be appropriately posed is why dedicate an entire book to such a rare tumor, and, for that matter, why expend so much effort and so many research dollars. The obvious first answer is the simple one: because people are suffering and they need our help. The more impressive argument is that the advances made in understanding this benign but debilitating disorder can be extrapolated to more common malignant tumors as well as to the common scar. The fact that desmoid tumors arise as a result of only a few mutations, as compared to the many different mutations identified in breast and colon cancers, simply makes the scientific exploration more straightforward. Further, the pathway implicated in the genesis of DT, the APC/β-catenin pathway, is thought to play a role in many solid tumors. Similarly, highlighting both the similarities and differences between desmoid tumors and scar tissue may one day result in treatments that improve healing.

There are many obstacles to overcome in trying to effect a change that will translate into more successful treatment of such a rare disorder. The first, of course, is recognition of the disorder, both for the individual patient and as an entity worth diagnosing and treating. The overwhelming consensus is that all desmoid tumor patients should be seen at a dedicated sarcoma center. However, there is often much confusion about the diagnosis and without a diagnosis such a referral will not be made. The different pathologic designations assigned to it, such as aggressive fibro-
matosis, deep fibromatosis, nonmetastasizing fibrosarcoma, Grade I fibrosarcoma, and musculoaponeurotic fibromatosis, add to the uncertainty. A very common story is that the patient is greeted in the recovery room by a smiling, confident surgeon who reassures the patient that there is no need for concern as it is just scar tissue or just some benign process.

After receiving such good news, many patients will not seek further medical followup until they become symptomatic. But even more horrifying than this benevolent neglect is the well-intentioned maiming of patients by surgeons who perform repeated resections in the hope of a cure. Repeated surgical trauma may make DT more aggressive and the pursuit of negative margins not justified in the face of great morbidity.

The disease entity as a whole suffers from the same lack of notoriety. Desmoid tumors are truly an orphan disease; even experts who dedicate their lives to combatting it cannot agree on whether it falls into the category of a sarcoma. Labeling it as benign or malignant creates false assumptions about its genesis and the natural course of this disease. One exciting development has been the acceptance of desmoid tumors into NORD, the National Organization of Rare Disorders. This organization is dedicated to advancing the cause of rare orphan diseases through education, lobbying of politicians, and promoting research. The quest for a cure has been further advanced by advocacy groups such as the Desmoid Tumor Research Foundation and SARC (Sarcoma Alliance for Research through Collaboration) in the US and Association S.O.S. Desmoide in Europe. Each year dozens of sarcoma advocacy groups exchange ideas and forge partnerships of collaboration at the CTOS (Connective Tissue Oncology Society) meeting.

The efforts expended in bringing together dedicated professionals and laypersons have translated into highly sophisticated and collaborative research in institutions across the world. The identification of Tumor Initiating Cells, or stem cells, in desmoid tumors may provide a therapeutic target. The elucidation of molecular pathways has already started to provide markers which will one day dictate the appropriate therapy individualized for each patient. Labs are sharing precious tissue samples and devising new techniques for amplification. Through the study of desmoid tumors, new forms of RNA have been identified that will have resounding ramifications throughout the research community.

Just as the number of desmoid patients is small, so is the community of professionals dedicated to finding a cure. Many of those brilliant clinicians and researchers contributed to this book. I would again like to thank each one of these contributors, all of whom did not hesitate to sign on, and challenge them to make the data presented in this first edition obsolete in the near future.
Part I

The Identification and Treatment of Desmoid Tumors
Chapter 2
Clinical Presentation of Desmoid Tumors

Anastasia Constantinidou, Michelle Scurr, Ian Judson and Charisse Litchman

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Abstract  Desmoid tumors (DT) constitute a rare fibroblastic proliferative disease. They present sporadically or as a manifestation of a hereditary syndrome such as Familial Adenomatous Polyposis (FAP). Despite the absence of metastatic potential, DT may cause debilitating symptoms and in some cases life-threatening organ damage because of their locally invasive nature. DT may range from small slow-growing masses to rapidly enlarging aggressive tumors. The clinical course of the disease is unpredictable but available data suggest an initial phase of growth may be followed by a long period of growth arrest with tumor stabilization or even regression. FAP-related DT are preferentially located in the abdomen whereas sporadic DT tend to involve mostly the extremities, although the abdomen and the thorax may also be affected. Antecedent trauma, pregnancy and estrogens play a role in the genesis of some desmoid tumors. Surgery is the favored current approach in the treatment of most desmoid tumors. Definitive protocols are not available as