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Foreword

The trajectory of modern cancer research has changed dramatically over the past four decades. The beginning of this time period can be demarcated with some precision—the publication by Varmus, Bishop and colleagues in 1976 that demonstrated that normal genes residing within our genome, proto-oncogenes, have the potential to be corrupted and become genetic agents that actively drive neoplastic cell growth, the oncogenes. This discovery led to a massive effort to document these genes during the following decades. By now, we are aware of more than 50 commonly occurring genes that can be documented, when in altered form, to function as oncogenes as well as an even larger cohort of genes that work in the opposite direction, the so-called tumour suppressor genes. Oncogenes become hyperactive in the genomes of cancer cells, whereas the growth-constraining actions of tumour suppressor genes are lost during tumour pathogenesis.

These discoveries led to a simple and powerful paradigm, specifically that the behaviour of cancer cells and the tumours that they form can be understood in terms of the mutant genes that they carry in their genomes. During the 1990s, however, diverse lines of research led to the realization that this paradigm represented a gross oversimplification, simply because cancer cells do not exist in a biological vacuum. Instead, as pathologists knew for a century, cancer cells reside in the complex tissues termed tumours, which, in addition to neoplastic cells, carry a variety of recruited host cells that together constitute the tumour-associated stroma. Indeed, the complex heterotypic signalling interactions between cancer cells and stromal cells led increasingly to the conclusion that the tumour stroma also represents a key determinant of tumour behaviour. Moreover, the variety of inflammatory cells recruited to the tumour stroma led to the simple conclusion that 'tumours are wounds that do not heal' and that the cellular and tissue programmes that enable the complex reconstruction of wounded tissues are co-opted by cancer cells—notably carcinoma cells—in order to progress to high-grade malignancies. As was learned in the first decade of the new century, signals released by recruited stromal cells can profoundly perturb the biological phenotypes of the cancer cells that previously recruited them.

Even this model soon required refinement, in that the perturbations of the systemic physiology of the host also required attention. Notably, cancer cells release systemic signals that enable them to perturb various components of the bone marrow, which in turn results in the mobilization into the circulation and subsequent recruitment of a variety of stromal cells that populate the 'reactive stroma' of an advanced tumour; such cells perturb the signalling environment of the nearby cancer cells that had previously recruited them into the tumour-associated stroma.

Even this depiction falls short of encompassing the full spectrum of complexity because of an additional facet of tumour/host interactions. Over the past decades, cancer biologists have repeatedly ignored the actions of the adaptive immune system in controlling tumour outgrowth. Many were persuaded that the immune system was tolerant to the presence of tumour-associated antigens and thereby ignored or overlooked tumour outgrowth. As we now realize, the absence of readily observable immune attack is often the result of multiple layers of defence that tumours mount to neutralize immune attack.

This immunological control of tumour outgrowth now begins to converge directly on the process that is the central theme of the current volume: how do disseminated tumour cells enter into dormancy, and how do the processes involved in treating primary tumours awaken them, resulting in life-threatening metastases? Why do disseminated tumour cells (DTCs) remain unapparent for days and months and then, either spontaneously or in response to certain perturbations, spawn rapidly growing metastases?

In the context of breast cancer pathogenesis, these questions are particularly acute. Perhaps one-third of breast cancer patients presenting in the oncology clinic carry myriad micrometastatic deposits of carcinoma cells in their marrow, and one-half of these women will eventually develop metastatic disease. Most interesting is the question of why the other half of women fail to do so. To be sure, the carcinoma cells in many micrometastatic deposits remain dormant and thus clinically inapparent because these cells, having arrived in the marrow (and in numerous other sites throughout the body), are poorly adapted to thrive in a tissue microenvironment that is foreign to them. After all, why should a mammary epithelial cell upon arrival in the marrow possess the traits that enable it to proliferate in such an unfamiliar and potentially inhospitable tissue microenvironment?

Yet another mechanism may explain the inability of the vast majority of DTCs to proliferate in sites of dissemination: the immune system may hold them in check. Such immune-imposed control may represent a centrally important mechanism that can be derailed by systemic perturbations, including those wrought by the wounding at distant sites associated with primary tumour resection and, perhaps more importantly, the postsurgical wound-healing response. Whilst the innate and adaptive arms of the immune system possess multiple mechanisms for recognizing and controlling the outgrowth of DTCs, their actions might be disrupted by countervailing mechanisms, specifically immunosuppressive mechanisms such as those exerted by regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs).

When depicted this way, the outgrowth of DTCs may be the result of a finely tuned balance between immunological attack and the immunosuppressive actions

that normally serve to hold immune attack in check. This balance may well be disrupted by the significant changes in bone marrow physiology that occur, usually transiently, in response to localized wound healing at various sites throughout the body. If demonstrated definitively, this leads to a notion that is likely to be accepted only reluctantly by many in the clinical oncology community: primary tumour resection does not provide an undiluted benefit to the breast cancer patient in terms of long-term survival, simply because postsurgical wound healing may upset the finely tuned physiologic balances that keep DTCs in check. Indeed, more extensive wounding and subsequent wound healing may result in an even greater likelihood of subsequent eruption of previously inapparent micrometastatic deposits. Various aspects of these fascinating interactions are described in this volume, which is likely to profoundly influence future surgical oncology and postsurgical treatment protocols.

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Preface

The authors of the chapters in this book are from the UK, USA, Italy, Nigeria, Australia, USA by way of Russia and Israel, UK by way of India, Denmark, Germany, Greece, and Belgium. One would think our intention was to have a geographically diverse representation of authors so as to get a worldwide perspective similar to the United Nations. But that was purely an accident. We did want a diverse group of authors and perspectives, but the topic for diversity was scientific investigation not geographic location.

Let us explain. Our research has been by discovery rather than hypothesis. We were trying to understand the implications of anomalous clinical breast cancer data. We did not know where it was taking us, but we just followed our scientific instincts. With the aid of knowledge from various medical specialties, mathematical tools and other resources, we have gradually come to the conclusion that something dramatic happens at or about the time of primary surgery that precipitates most relapses in breast, lung and other cancers.

It also seems that this effect was known 2000 years ago but somehow got overlooked. Regardless of that, this topic must be considered a new field. Hopefully, this book will stimulate new thinking and the generation of new data.

We looked around. Who else is doing some work that may be related to what we have found about the perioperative window? It turned out that there are some. What scientific tools are used? All available tools! Actually, the diversity of tools and approaches attracted us since we promoted to the publisher that this book would be a jumping-off point for continued research as well as a reference for clinicians and scientists. We wanted to be inclusive with minimal overlap of research or clinical specialties. We have already crossed several medical boundaries so that is no longer a barrier.

There are a number of possible mechanisms that could account for this effect, but we do not know which are most involved or even if we know them all. We do know that systemic inflammation plays a key role and that this lasts for about 1 week after surgery. We think the metastatic initiation process is amplified by approximately 100-fold during the week post-surgery. Based on a retrospective study, a perioperative anti-inflammatory intervention properly timed to the surgery would probably

prevent early relapses and that these would not come back later. We strongly recommend that this needs to be verified, and if it works as we think, it could reduce the world's breast cancer problem by 25–50% at almost no cost or toxicity. Some egos will be bruised, and pocketbooks will be lighter, but that should not prevent this investigation from being pursued.

Sub-Saharan Africa would be an ideal place to conduct a clinical trial because of the high incidence of triple negative breast cancer (TNBC) since that category should respond best to a perioperative NSAID. Breast and lung cancers have been the most investigated, and there are a number of other malignancies for which this should also work, but evidence has not as yet been fully examined. This type of therapy would be ideal for developing countries where there is 70% of the cancer burden but only 5% of the resources.

It needs to be stated that even if this project works as well as possible, it will not solve the cancer problem. It will dramatically and inexpensively reduce the number of patients who relapse, but there will still be a need for treatments to prevent death from metastatic disease. We are not in competition with the excellent work underway to use immunotherapy to curtail tumour growth after relapse.

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Introduction

Chapter 1. We have been collaborating on a cancer research project that will be discussed in this book that can trace its origin to an event in 1993. Retsky was attending a cancer conference in Europe and happened to notice a poster in the hallway outside the lecture hall presented by Demicheli. The poster showed a bimodal relapse hazard for patients treated at Demicheli's institution in Milan. The patients (N = 1073) were treated with mastectomy after diagnosis of breast cancer and followed up for over 15 years. These data were intriguing in that there was apparently a wave of relapses in the first 3 years after surgery, then there was a period at 4 years with few relapses, and that was followed by a second wave of relapses that had a shallow peak at about 5–6 years after surgery and continued for 15 and more years.

Retsky had been doing research in breast cancer for about 10 years prior to this time, and Demicheli was on the staff of Milan National Cancer Institute as a clinical researcher for longer than that. Retsky had never seen data such as Demicheli was showing.

It is not incidental, but as we discovered later, both Retsky and Demicheli have PhDs in physics (Demicheli also has an MD). Among many other descriptions, physics is a way of thinking, and pursuing the implication of anomalous data plays a central role. To illustrate, the most important discoveries by the most highly regarded physicists in history can be traced to understanding the meaning of anomalous data.

For one example of the importance of anomalous data in scientific discovery, in the 1600s, Tycho Brache spent a number of years recording the position of the planets visible to him relative to the sun. Brache never got enough credit for what happened next, but Johannes Kepler obtained Brache's data and analysed it and to his surprise found the trajectories have distinct similarities that he reported as what are now known as Kepler's Laws. As one of these laws, Kepler found the planets orbited in an elliptical path with the sun as one of the two focal points. As another law, Kepler reported that the area swept by the planet's orbit per unit of time was constant. The third law was that the square of the period of the orbit was proportional to the cube of the semi-major axis of the ellipse. Isaac Newton considered these laws of Kepler based on the data from Brache and after inventing calculus derived

the famous result that gravity holds the planets in their orbits with an inverse square dependence on separation and is proportional to the product of the masses of the sun and the specific planet.

As another example, in 1887, Michelson and Morley were measuring the velocity of light from different stars and found to some amazement that the velocity of light did not depend on the velocity of the star relative to the Earth. Albert Einstein considered that and ultimately derived the dramatic law of Special Relativity in 1905.

Not to place ourselves in the same category as Newton and Einstein, this serves to show the historic importance of pursuing anomalous data in the field of physics. Getting back to Demicheli's poster showing a bimodal relapse pattern, this was important anomalous data in breast cancer. Retsky and Demicheli spent the next two decades trying to interpret what the bimodal relapse data were telling us.

This bimodal pattern of hazard of relapse among early-stage breast cancer patients has now been identified in multiple databases from the USA, Europe and Asia. We are studying these data to determine if this can lead to new ideas on how to prevent relapse in breast cancer. Using computer simulation of this very high-quality database from Milan for patients treated with mastectomy only, we proposed that relapses within 3 years of surgery are stimulated somehow by the surgical procedure. Most relapses in breast cancer are in this early category. Retrospective data from a Brussels anaesthesiology group suggested a plausible mechanism. The use of ketorolac, a fairly common NSAID analgesic sometimes used before and after surgery, was associated with far superior disease-free survival in the first 5 years after surgery. The expected prominent early relapse events in months 9–18 are reduced fivefold in the Brussels data. Transient systemic inflammation accompanying surgery (identified by IL-6 in serum) could facilitate angiogenesis of dormant micrometastases, proliferation of dormant single cells and seeding of circulating cancer stem cells (perhaps in part released from the bone marrow) resulting in early relapse and could have been effectively blocked by the perioperative anti-inflammatory agent. If this observation holds up to further scrutiny, it could mean that the simple use of this safe, inexpensive and effective anti-inflammatory agent at surgery might eliminate early relapses. We suggest this would be most effective for triple negative breast cancer and would be especially valuable in low- and middle-income countries. Similar bimodal patterns have been identified in other cancers suggesting a general effect.

This will be discussed in detail in the following chapters, but the point we wish to make here is who best could we ask to discuss this? We have already invited Robert Weinberg who is perhaps the world's most renowned thought leader in cancer biology to write a foreword for this book. Who do we know in the clinical realm with the proper background to think in the manner needed to put this in perspective? The answer of course is our cancer researcher, medical historian, philosopher and breast surgeon colleague Michael Baum who has written extensively on this subject.

In Chap. 1, we present excerpts from Michael Baum's publications that have been strung together to provide a chronological narrative that relates to the topic that

is the central theme to be discussed in this book. Some of the texts in this chapter are taken verbatim, and other texts are modified from references 43 and 48–50 in the chapter by Baum. In addition, at the end of his chapter, Baum has added some fresh insights that challenge the received wisdom of the somatic gene mutations as the driving force of oncogenesis and how indirectly it provides some insights into the nature of the anomalous observations that have provoked us to produce this book.

Chapter 2 is written by editor Retsky and coeditor Demicheli that we hope will adequately sum up our knowledge base on this subject.

Chapter 3 is written by Georgios K. Georgiou and Evangelos Briasoulis. We predicted that primary surgery would initiate angiogenesis so we were much interested in a study that dealt with this. Georgiou and Briasoulis looked ideal to write a chapter describing their project. They measured circulating angioactive factors in blood before and after surgery in women with breast cancer and in other women with non-malignant fibroadenoma. It is a small study, but they find intriguing results. We hope that this study motivates others to conduct larger studies since there is much to learn. We note with regret that the initiator of this project, Prof. Briasoulis, died recently from cancer of unknown primary.

Chapter 4 is by Jonathan Hiller, Robert Schier and Bernhard Riedel. The chapter by Hiller et al. discusses the perioperative window from the perspective of clinical anaesthesiology. This would be a good place to start reading on a major clinical component of this book. The authors present the science and practice of anaesthesiology in cancer surgery with emphasis on the teleological aspect. This fascinating viewpoint describes our ancestral hard-wired response to trauma, injury and infection and how this impacts the oncologic effect of surgical removal of malignancy. Note in particular the section on NET (neutrophil extracellular traps) that trap bacteria and parasites but quite interestingly circulating cancer cells. This seems to be one of several processes involving neutrophils reported in this book that could explain surgery-induced metastatic activity. We were quite taken by a comment in Hiller et al. (2013) in *Best Practices* that ‘The perioperative period can be considered a ‘perfect storm’ of immunosuppression and inflammation in the presence of residual or circulating tumour cells’.

Chapter 5 is written by Mazen A. Juratli, Dmitry A. Nedosekin, Mustafa Sarimollaoglu, Eric R. Siegel, Ekaterina I. Galanzha and Vladimir P. Zharov. When we started this project, the original computer simulation used a time increment of 5 days. That is, the simulation updated tumour size and other malignant processes every 5 days. We thought that was reasonable given that breast cancer takes at least 10 years to run its course. But now, we think just after surgery things happen very rapidly. Thus, one of our criterions for these chapters was to include some research activity dealing with cancer development involving perhaps circulating tumour cells or initiation of capillary leakage with time scale of fractions of 1 day. The chapter by Juratli et al. fits that description. They describe some interesting technology that can measure circulating tumour-cell activity within minutes of a biopsy or surgical intervention. Their experiments are on mice, but we are told as of this writing that the authors are obtaining data from cancer patients. We look forward to their publications.

Their animal data show evidence of tumour cells injected into circulation from biopsy but do not show cells injected into circulation from tumour surgery. This is consistent with data from delayed reconstruction compared to reconstruction performed currently with mastectomy as reported by Dillekas and Demicheli et al. in a Norwegian study. The paper by Dillekas and Demicheli et al. is discussed in both the chapter by Retsky-Demicheli and the chapter by Vaidya. It is good to see a correlation between animal models and clinical data.

Chapter 6 Osaro Erhabor et al. This chapter is a dramatic and sobering document that should be required reading for any researcher who is planning or even thinking about conducting a clinical trial in Nigeria or sub-Saharan Africa. Retsky has been in Nigeria twice in the past few years and will be there again soon. Several things need to be discussed.

There is considerable redundancy in this chapter. For example, 'triple' appears 16 times. It was apparent to Retsky in editing that 4–6 individuals each wrote portions of this chapter that were more or less patched together to make the document. This is an advantage to us in that we get a number of independent scientific/medical viewpoints on breast cancer from clinicians and other professionals from various sections of western Nigeria. There are different opinions on what needs to be done, but every one of the authors reports triple negative breast cancer is the dominant type in their community and is a major therapeutic challenge. Presentation with locally advanced cancer is common, and it seems that women fear mastectomy and choose to avoid it for a variety of reasons.

They are requesting help from the West in solving the poor outcome for many women in Nigeria. That is extremely well justified in our opinion, and we would add that this could be an *opportunity* for the West to learn how to better treat TNBC. If we could learn how to treat TNBC in Nigeria, it would be a major help to treating all types of breast cancer in all countries in the world whether resources are limited or not. Based on Retsky's participation in cancer patient web-based groups, he does not want to mention names, but there are places in the world including the USA that are not too dissimilar to Nigeria.

In Nigeria, Retsky would frequently walk around alone and can personally verify that, as indicated in the chapter, there are shanty towns where street names and addresses are absent. As noted in the chapter, it will be difficult to follow up patients if you cannot locate their residence. Thus, some patients will be lost to follow up, and that needs to be considered in trial design. However, Nigeria has a diverse socio-economic population, and there are other areas where communities look identical to those in upper-scale USA.

Chapter 7 Hanin. This paper includes some mathematical equations and will scare away many readers. Hanin is originally from Russia, and as a general statement many Russians seem to love mathematics. Retsky has seen many older papers with extensive mathematical equations published by Russian authors that mention cancer in the title and in the first and last paragraph but nowhere else. The paper by Hanin uses mathematics, but the author actually uses it to analyze clinical data. He raises an interesting clinically relevant question. The reader may not need to

understand details of the mathematics but should know enough to capture the author's intent and may cause him or her to think about this issue.

That leads to another reason why we include a mathematically oriented document here. Mathematics is considered the Queen of Sciences, but it seems to us that it too rarely appears in biological science papers. That is changing, and we hope this chapter will add more interest in the use of mathematics in clinical cancer research.

Chapter 8 Marie L. Bønnelykke-Behrndtz, Henrik Schmidt, Yi Feng, and Paul Martin. We wanted to include several chapters that deal with animal models and cancer. The chapter by Bønnelykke-Behrndtz et al. intrigued us since it used zebrafish models that are translucent and it also reported a new mechanism that might explain surgery-induced metastatic activity in a melanoma model. This mechanism involves neutrophils that are discussed again in the chapters by Forget and De Kock and by Hiller et al.

The mechanism seen in zebrafish is that preneoplastic cells attract neutrophils resulting from systemic inflammation. The preneoplastic cells then start dividing. This is an intriguing effect. This was one of the chapters we submitted to Prof Bob Weinberg to provoke his thoughts in writing the foreword. Bob Weinberg has been very helpful over the past years in this research. It has been extremely valuable to bounce these counterintuitive ideas off a world-renowned cancer biologist.

It is only at the talking stage, but there is interest in a possible paired clinical trial of perioperative NSAID for breast cancer in Denmark and in Nigeria. Both countries would have the same or nearly same protocol, and the trialists would meet occasionally. Denmark has the highest incidence of breast cancer in the world, and health care is provided by the government so it is easy to understand their particularly high interest in reducing the morbidity and mortality from that disease.

Chapter 9. Patrice Forget and Marc De Kock. That something happened at or around the time of surgery to provoke early relapses was strongly indicated, but up until 2010, we had only vague notions of mechanisms and much less in the way of ideas on how to prevent these from occurring. A paper by Patrice Forget and Mark De Kock in 2010 produced a revolutionary change in our thinking. This is described in the chapter by Retsky-Demicheli.

To present an interesting descriptive event, Patrice Forget came to Boston with his family during the summer of 2012 or 2013 for a month. Retsky arranged meetings and seminars with some Harvard and MIT groups. One meeting in particular occurred at MIT where Retsky and Forget each gave 20-min presentations on the breast cancer project to a small group of postdocs and students at the Broad Institute. The moderator of the meeting was postdoc Jordan Krall of Weinberg's lab who is now doing some experimental work in this field. Retsky gave his talk and Forget did likewise. Questions were then invited. One person sitting in the back row said, 'Breast cancer is a disease that runs its course in over 10 years. Are you telling us that most of the events leading to relapse years later occur in the first week after surgery?' That short comment captured the essence of our research! We never did get this person's name, but we have used that comment in one form or another in our papers since then. After the meeting, Retsky reported that episode by e-mail to his colleagues in distant cities and countries. Mike Baum wrote back that this was an

example of ‘the butterfly effect’. In case you do not know what that means, it refers to the comment that a butterfly might flap its wings in Mexico and cause a thunderstorm in Canada. It may indeed turn out to be scientifically possible, but on the surface, it is a preposterous connection. This book was almost titled ‘Breast Cancer and the Butterfly Effect’.

It is a pleasure to introduce this chapter by Forget and De Kock. What are they working on now? They discuss the neutrophil to lymphocyte ratio (NLR) that shows relevance as a preoperative biomarker of systemic inflammation for breast, renal and lung cancers. They also report on short-term morbidity (septic and cardiovascular) and long-term mortality from cardiovascular disease (after lung cancer surgery and after hip fracture). Forget and De Kock suggest there is a need for new biomarkers and a need for a paradigm shift, and they have been right in the past.

Forget and De Kock also discuss postoperative peripheral neuropathy as a possible result of systemic inflammation. Permit Retsky to provide a patient’s perspective on postoperative peripheral neuropathy. He is a long-term survivor of stage IIIc colon cancer and is a founder and director of the Colon Cancer Alliance. For several years, he participated in web-based discussion groups for colon and breast cancer patients. Among fellow cancer patients, they would candidly discuss intimate details of their disease and treatment. (Retsky recommends that lab-based cancer researchers join a patient website—as a lurker—with permission of the site ‘owner’. They will learn much about clinical cancer.)

Richard Farrell was also a patient and founder of the Colon Cancer Alliance. Richard who ultimately died from metastatic colon cancer was very open with his cancer experience especially after he relapsed with hepatic metastases. The situation is better now, but 20 years ago, hepatic relapse was almost always fatal. He lived in Pennsylvania and since retirement was a very active fisherman. He would catch and release—not wanting to kill fish for sport. Richard knew where his disease was heading, and to aid fellow patients, he would frequently discuss his situation openly so they could benefit from his experience. He would ominously begin his reports with ‘The journey continues…’. At one point, he was operated upon by a well-regarded hepatic surgeon at Memorial Sloan Kettering Cancer Center. The patients would often discuss both good and bad skills of surgeons and staff in detail. So we all knew Richard was getting extremely competent treatment. (The point of this story will become apparent later.)

Richard’s surgery was considered successful, and he lived another year before eventually dying from metastatic colon cancer. He reported on the patient website that treatment at MSKCC was first class, but he also noted that after recovery he had peripheral neuropathy. Retsky remembers speaking to Richard about that. They happened to meet on a train station waiting for a train to a meeting somewhere and had a chance to talk. Retsky was curious about the peripheral neuropathy. Richard was operated upon whilst lying flat on his back with arms spread out. The operation was 6 or 8 h long. The explanation given to him afterwards was that someone must have been leaning over the operating table and inadvertently cut off circulation to his hands for extended periods of time, and that caused the permanent nerve damage in his hands.

We need to emphasize that this was not a life and death situation. It was only a quality of life side effect. Richard could not button a shirt, tie his shoes or much less go fishing for the year he lived after the hepatic surgery. Retsky had never heard about peripheral neuropathy before, and this stuck in his mind. Why did this happen in both hands he wondered. He asked Richard if he could tell this story to others. Not surprisingly, Richard emphatically gave Retsky permission to do so.

In 2010, Retsky happened to see a paper from a group at Mayo Clinic on postoperative peripheral neuropathy (Staff et al., 2010) describing it as mainly inflammation driven. He wondered if this could explain what happened to Richard Farrell. He asked the question and passed the paper to Patrice Forget. Forget replied probably so but such an effect is quite variable from one case to another. This paper is discussed in the chapter by Forget and De Kock. During Retsky's review of the chapter by Vaidya, he also sent the paper by Staff et al. to him.

Retsky does not want to go into details here but suspects there is a connection among the chapters by Forget and De Kock, by Vaidya and Richard Farrell's perioperative neuropathy. The medical issue involved is mortality from cardiac disease soon or even years after surgery as the result of inflammation-driven postoperative neuropathy.

Chapter 10. As coeditor and equal partner in the breast cancer project, Demicheli dives deep into the cancer biology literature and reports that cancer in the undisturbed state shows some similarity to normal tissue and organs. It may be closer to normal than usually thought at least in that undisturbed state.

Chapter 11. Vaidya. The chapter by Jayant Vaidya starts far removed from the subject of this book. It considers two separate subjects: first, there is consideration of breast reconstruction after mastectomy, and second, there is consideration of intraoperative radiation instead of external beam radiation to prevent local relapses after lumpectomy. How each of these diverse subjects arrives at useful information regarding intervention-induced inflammation and early relapse is a remarkable story. As someone who considers himself quite skilled in extracting all the useful information possible from data, Retsky is impressed with the project described in this chapter.

In addition, as soon as it gets to be public knowledge, it will be an important clinical issue. Imagine that each year for the past few decades, it is possible that over a thousand people have died from previously unknown side effects of breast cancer treatment. Furthermore, this may be connected to the Richard Farrell peripheral neuropathy and likewise be simply testable and resolvable. Clinical trials in most cancers including breast do not include all-cause mortality, only breast cancer-specific mortality. From the lessons of this chapter, that may need to be reconsidered.

There is no need to say anymore. Read the chapter by Vaidya and experience scientific discovery and excitement at a very high level.

Chapter 11
The Systemic Effects of Local Treatments (Surgery and Radiotherapy) of Breast Cancer

Jayant S. Vaidya

Abstract In general, treatment of solid tumours has been compartmentalized as local treatment and systemic treatment. The only systemic oncological effect of local treatment is supposedly eradication of the primary cancer thereby reducing the probability of further systemic spread. However, as will be described here there are instances where local treatment could impact the outcome in diverse ways. We describe how the modulation of surgery by changing its extent or addition of intra-operative radiation appears greatly impact it systemic effects.

Keywords Breast cancer • Lumpectomy • Targeted intraoperative radiotherapy TARGIT IORT • Relapse • Mastectomy • Reconstruction • Non-breast cancer deaths • Mammoplasty • Surgical trauma

11.1 Clinical Observations

11.1.1 Larger Extent of Local Surgery Appears to Paradoxically Worsen Surgical and Cancer Outcomes

In recent years, the development of new surgical techniques and the availability of newer implant materials has meant that there are increasing numbers of immediate breast reconstruction procedures that allow a woman to wake up after her mastectomy with a newly created 'breast'—a proposition that is attractive to many women facing a diagnosis of breast cancer as well as surgeons performing such a mutilating operation as a mastectomy. A Cochrane review [1, 2] attempted to establish whether there is any demonstrable patient benefit (e.g. psychological) from such procedures

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but found no clear evidence to support immediate reconstruction over delayed reconstruction [1]. In another study, the psychological distress at 1 year for immediate or delayed reconstruction was found to be similar to each other and to those who did not have any reconstruction [2]. However, the benefit of performing a breast reconstruction after a mastectomy appears to be considered so obvious that, unlike most other breast cancer treatments, no good randomised evidence has been sought before widespread acceptance and adoption of various reconstructive techniques.

However, such a strategy ignores the fact that many of these take much longer to perform and involve extensive dissection of either local tissues or distant tissues (such as the latissimus dorsi flap or the deep inferior epigastric artery perforator flap—DIEP). New evidence is emerging that suggests these extensive surgical procedures at the time of surgical extirpation of cancer may not be oncologically safe. An interesting non-randomized study comes from the University of Ireland and involved 229 patients. These breast cancer patients underwent immediate breast reconstruction between 2004 and 2009 and the authors found that 23% of patients suffered a wound complication. This complication rate is much higher than seen when only a mastectomy without reconstruction is performed, when it, is usually less than 5%.

Many would suggest that this complication rate is unusually high, but in a more recent study (a rare randomised study published in December 2016) a large Scandinavian collaborative group reported in Lancet Oncology, the first randomised trial of immediate vs. delayed reconstruction with implant + acellular dermal matrix [3], a highly commendable effort. This 142-patient trial had to be stopped early because the Data Monitoring Committee felt it was not safe to continue. When immediate reconstruction was performed, there were many more complications (46% of cases) and re-operations (37%), compared with delayed reconstruction (18% and 15%). So, the high complication rate in the Irish study was not unique.

The most worrisome observation in the Irish study was that those patients who had complications had a significantly lower 5-year relapse-free survival (64%) compared with those without complications (89%), a large difference that could not be explained by any patient or tumour factors. The authors suggest that the increased inflammatory response incited by the wound complications may be detrimental to cancer survival [4]. It will be important to assess breast cancer and non-breast cancer survival in the longer term in the Scandinavian randomised trial to determine if any effect of the complications and timing of reconstruction is evident on oncological outcomes, although the small size of the study may limit the ability to detect all but large differences.

A similar picture appears to arise in the delayed reconstruction setting. A case-controlled study [5] performed in a University Hospital in Norway between 1977 and 2007 which compared 312 patients with delayed reconstruction with 1341 matched controls found a remarkable peak hazard of relapse 18 months after reconstruction, similar to that normally observed at a similar time after the primary surgery. The authors also found that, ‘the more extensive reconstruction modalities DIEP/TRAM procedures give rise to a higher early peak in comparison with unilateral implant surgery’. Such a dose-response relationship is usually characteristic of a causal link. They concluded that ‘reconstructive breast cancer surgery constitutes

an independent stimulating event on the growth of micro-metastases leading to accelerated relapse rates.'

These studies raise the real concern that increasing surgical trauma and perioperative inflammatory response may be triggering the growth of metastatic disease.

11.1.2 Local and Systemic Effects of TARGIT Intraoperative Radiotherapy Given during Lumpectomy for Breast Cancer

The clinical data in the breast reconstruction studies appears to be supported by laboratory findings looking at wound fluids that collect in the cavity left behind after a lumpectomy. These experiments were performed within the context of clinical trials of targeted intraoperative radiotherapy (TARGIT- IORT) for breast cancer.

In one study [6] that included patients receiving TARGIT IORT, fluid collected in the wounds of patients undergoing TARGIT IORT immediately after a lumpectomy for breast cancer was compared with fluid from those having just lumpectomy. The authors found that wound fluid from normal wounds stimulates cancer cell growth, motility and invasiveness. Remarkably, such stimulation is nearly completely abrogated when targeted intraoperative radiotherapy is given during surgery. There is a sea change in the constitution of the wound fluid in those who receive TARGIT IORT compared with those who do not. These results have been since replicated eight years later, by Zaleska et al. [7] with different experimental conditions.

There also seems to be clinical evidence to suggest that this effect seen in the laboratory may translate into clinical outcomes since the wound fluid is normally absorbed into circulation and it has been postulated that it could have systemic beneficial effects [8]. In the TARGIT-A trial [9–13], 3451 patients undergoing lumpectomy for breast cancer were randomly allocated to receive either TARGIT IORT or whole breast external beam radiotherapy. In the analysis of deaths, there was no difference in breast cancer mortality, which was low in both arms of the trial. However, the trialists found a significantly lower non-breast cancer mortality for the TARGIT IORT patients (HR. 0.47; $p = 0.0086$). The most likely explanation might be due to avoidance of whole breast irradiation. It has long been recognised that inadvertent irradiation of the lung, oesophagus and heart during tangential field radiation of the breast leads to fatal cancers and deaths due to ischaemic heart disease. Therefore, targeted radiation would avoid such deaths. This view has been vindicated by a meta-analysis of randomised trials [14] of targeted vs. whole breast external beam radiotherapy (EBRT) which found that in the breast cancer populations where the breast cancer mortality is low (about 5%), the deleterious effect of whole breast radiation is unmasked and leads to an increased overall mortality—thus using targeted radiation rather than whole breast radiation in such patients leads to an improvement in overall survival albeit by a small absolute amount (Figs. 11.1 and 11.2).

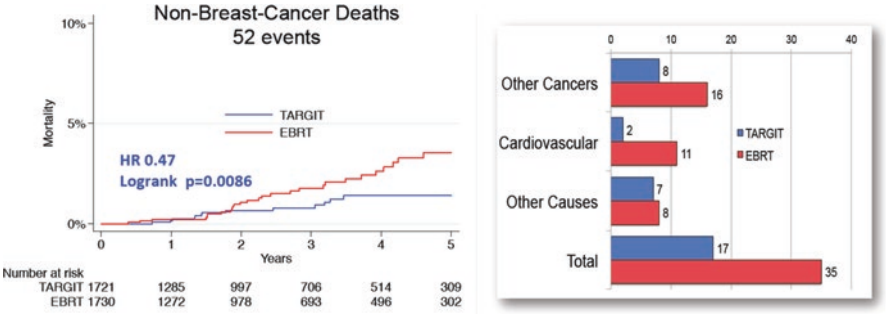

Fig. 11.1 Kaplan-Meier plot for deaths from causes other than breast cancer (17 vs. 35) in the randomised TARGIT-A trial, showing a significantly higher risk of non-breast-cancer mortality with whole breast fractionated radiation given postoperatively over several weeks (EBRT), compared with a risk-adapted single dose radiation delivered to the tumour bed during the lumpectomy operation (TARGIT) [10]

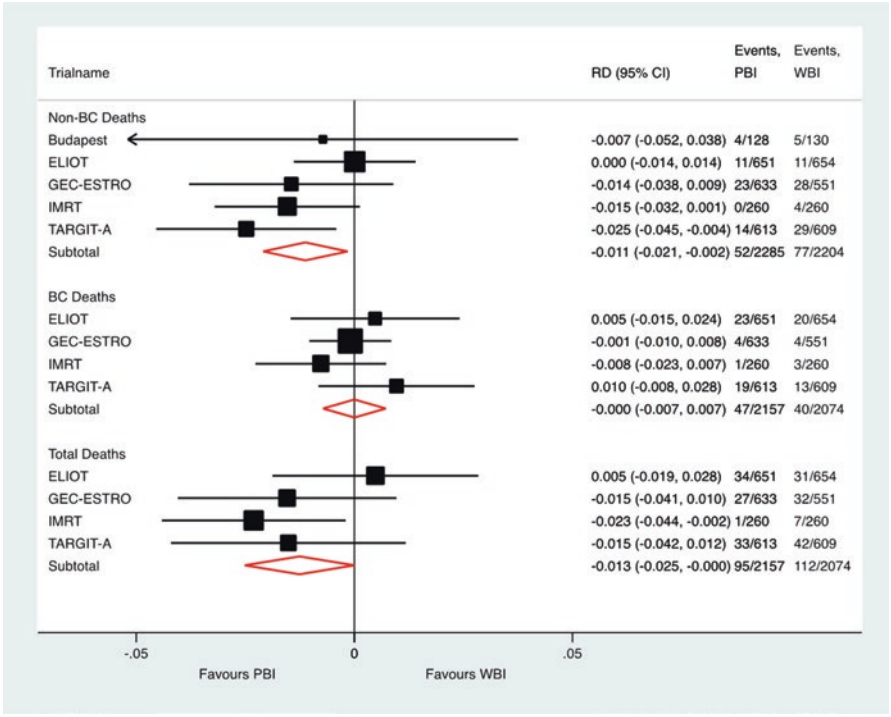

Fig. 11.2 Forest plots representing meta-analysis of difference in mortality between partial-breast irradiation (PBI) and whole-breast irradiation (WBI) with a random-effects model. The trials included for non-breast cancer (Non-BC) mortality were the Budapest trial [5], TARGIT-A [3], ELIOT [6], IMRT [8], and GEC-ESTRO [9]. The median follow-up of all these trials was 5–6 years. Data from only the initial 1222 patients in the TARGIT-A trial, whose median follow-up was 5 years, were included [14]. The Budapest trial was not included in the analysis of breast cancer (BC) deaths or total deaths because these figures were not available

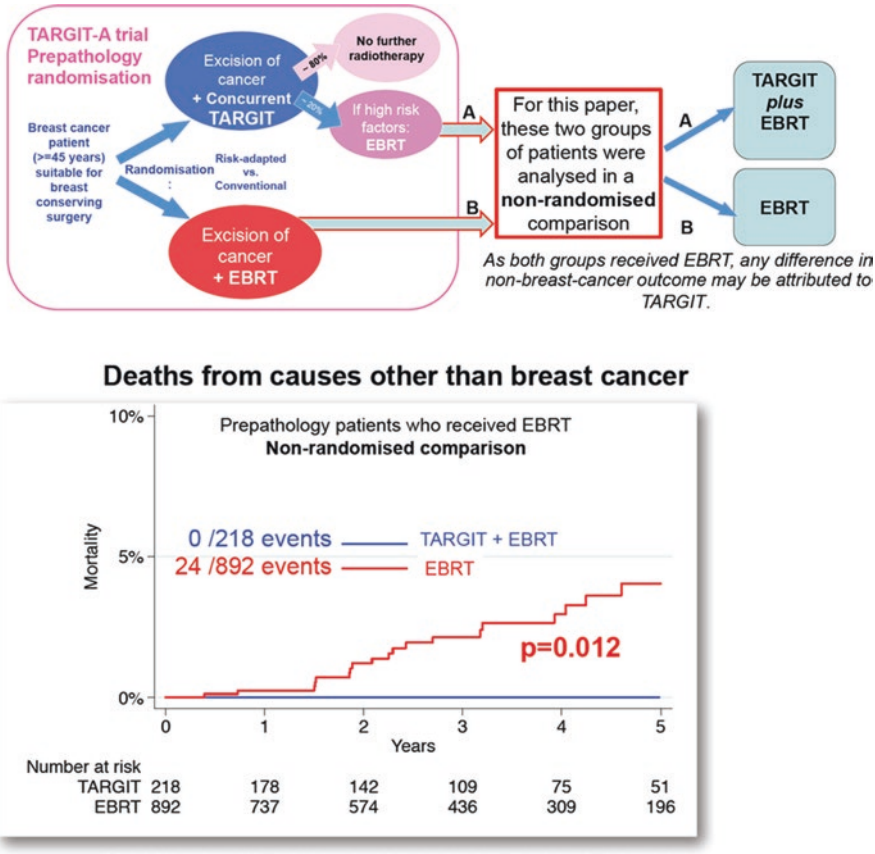

Fig. 11.3 Non-randomised comparison between those who received TARGIT + EBRT and those who received EBRT for deaths from non-breast-cancer causes: (*above*) schema of the analysed cohorts of patients; and (*below*) Kaplan–Meier plot depicting deaths from causes other than breast cancer in prepathology patients who received EBRT—non-randomised comparison [13, 14]

However, there is a twist in the tale. Could the difference in mortality plausibly be due to a *beneficial* effect of TARGIT-IORT, possibly due to its suppression of the cancer-stimulatory effects on the wound fluid? In the TARGIT-A trial, if TARGIT IORT was given concurrently with lumpectomy and if high risk factors were found subsequently, whole breast radiotherapy was added in about 20% of cases—all as specified in the original protocol which followed a risk-adapted design. Therefore, there was a cohort of patients who were randomised to TARGIT IORT and who received both TARGIT IORT and EBRT (Fig. 11.3) as per the protocol.

To try and understand the reason for the difference in non-breast-cancer mortality, a separate analysis [15] was performed: survival from causes other than breast cancer was compared between the two randomized arms but limited to those who had received EBRT. Therefore, the control arm included patients who were allo-

cated EBRT and received EBRT, and the experimental arm included patients who were allocated TARGIT and also received EBRT. The group that received TARGIT + EBRT was characterised by worse prognosis breast cancer but would not be expected to be different—certainly not better—than the rest of the cohort in terms of non-breast cancer co-morbidity, and as both groups received EBRT, any difference found in non-breast-cancer mortality could be attributable to the delivery of TARGIT IORT during lumpectomy.

The remarkable finding was that were no deaths from non-breast cancer causes in the TARGIT + EBRT group compared with 24 in the EBRT group 0/218 vs. 24/892, log-rank p = 0.012. Although the numbers are small and the compared groups are not the full randomised cohorts, these data suggest that EBRT toxicity may not be the only reason for the fewer non-breast cancer deaths with TARGIT IORT, and leads to the hypothesis that the local effect of TARGIT on the tumor bed by inhibiting the cancer-stimulating cytokines, may spill over to reduce systemic inflammatory response to trauma and have significant long-term systemic beneficial effects, that might be protective against cardiac and cancer mortality [8].

A more recent case control (non-randomised) study, also found that amongst patients having oncoplastic breast conserving surgery after neo-adjuvant chemotherapy, those who had an intraoperative TARGIT Boost, experienced better survival outcomes than those who received a postoperative EBRT boost (overall survival 96.7% vs. 81.7%, hazard ratio 0.19, log rank p = 0.016, and distant-disease free survival 95.1% vs. 69.0, HR 0.23, log rank p = 0.012) [16].

11.1.3 Causality

The scientific principle for establishing causality is firstly to show that the factor is present when the effect is seen, secondly to show that increasing amounts of factor increases the effect and finally, removal or abrogation of the activity of the factor reduces the effect. Thus, biologically, it appears that increasing surgical trauma is detrimental to outcome after local treatment of cancer and, if the systemic effects of such trauma are reduced, they may be improved. There have been some data that administration of non-steroidal anti-inflammatory drugs in the peri-operative period reduces mortality from solid tumours [17, 18]. A randomised trial is underway in Belgium to test this hypothesis.

11.1.4 Clinical Implications

The obvious benefit of waking up after a mastectomy with a new breast rather than a flat chest needs to be weighed against the need for a larger operation with the higher risk of complications, longer convalescence, delay in chemo/radiotherapy, with its well known detrimental effects, and the need for several further operations.

From the patient's perspective, a decision about having immediate reconstruction is usually confounded by the significant shock of a new diagnosis of breast cancer and the prospect of removal of the whole breast. A nudge in the direction of "reconstruction is the norm" may be enough to sway someone whose main concern is surviving from the cancer to get convinced that she needs to have it at the time of the mastectomy. The availability of reconstruction can appear to make the prospect of a mastectomy acceptable, even when it is not indicated for oncological purposes. Before all these remarkable data were available and notwithstanding the lack of benefit seen in the Cochrane overview and other studies, it seemed appropriate to offer breast reconstruction as a reasonable option (from both the clinician and patient perspectives) during discussions about mastectomy. Such discussions would centre around patient preferences only, as there was not much evidence either for or against until now.

The same arguments also lead to concerns about the rising trend of using mammoplasty during breast conservation as well as cosmetic operations on the contralateral breast as part of treatment of breast cancer. To us surgeons, the justification for these procedures is 'obvious'—a 'better' cosmetic outcome. Unfortunately, there is a well-recognised lack of good evidence to support the use of major oncoplastic procedures aimed at a better cosmetic result, either for oncological safety or even an improved patient satisfaction about cosmetic outcome [19]. Firstly, potential harms may arise from the additional burden about decisions about a bigger operation, yet another operation, longer recovery, reduced or loss of nipple sensation, psychological distress of decision about the other breast, as well as from the possible oncologic risks of increased surgical trauma and accompanying increased chance of surgical complications. Arguably, if the patient had been keen to have a cosmetic operation, she could have well considered it before the cancer diagnosis. The oncological safety of these more extensive procedures [6] has not been established in randomised clinical trials. One large series from a pioneer in the techniques reports a 5-year recurrence rate of 9.4% [20] which is several times higher than expected, although the authors suggest that the larger size of cancers or extensive DCIS may contribute to the higher recurrence rate. Another study found that use of implants is associated with poorer survival from subsequent breast cancer [21]. A recent study of lipofilling [22] found a high recurrence rate of 1.5% per year (i.e. 7.5% at 5 years). An accompanying editorial from Memorial Sloane Kettering Cancer Centre [23] has warned about the lack of oncological safety and recommended that lipofilling should not be performed outside a clinical trial. Most importantly, patient satisfaction appears to be similar with simple lumpectomy vs. therapeutic mammoplasty [24].

Postoperative radiation may affect the heart in many ways—the coronary arteries causing ischaemia, the muscle causing cardiomyopathy or even the nerves (neuropathy) and the conducting system of the heart, although we cannot find any previous mention of the latter in the literature. One speculation is to consider that post-surgical or post-radiotherapy cardiac neuropathy may be another possible mechanism to explain cardiac mortality as a result of breast cancer therapy. As suggested by Michael Retsky, we are aware that surgery can result in transient systemic inflammation and post surgical peripheral neuropathy has been associated with

inflammation [18, 25]. As a possible connection among these effects, immediate irradiation of the surgical wound may contribute to a reduction in inflammation thereby reducing cardiac damage.

Given the new randomised evidence demonstrating a higher risk of complications, as well as evidence suggesting a real possibility of an oncologically detrimental effect of excessive trauma, the most prudent clinical approach is to ensure that patients are fully informed of the evidence that raises a doubt about the oncological safety of therapeutic mammoplasty procedures and breast reconstruction, along with a lack of benefit in terms of patient's satisfaction or psychological parameters.

A material change in relationship between a doctor and a patient has occurred with the publication of the United Kingdom ruling of the Montgomery vs. Lancashire case in early 2015. It is important to recognise that although this is law only in the UK, it could have far reaching implications around the world. The ruling sets a precedent over the process of obtaining informed consent and the need to discuss all options of treatment that the patient may consider reasonable. This is now a legal responsibility rather than just a moral duty and the final decision over the correct application rest with the Courts and not with the medical profession or with patient advocacy groups. Breast surgeons and staff must move away from a single 'recommendation' but offer a list of evidence-based options for patients to consider, along with their risks and benefits. This has wide ranging implications in surgery, particularly in the practice of oncoplastic breast surgery, largely because of near-complete lack of level-I evidence across the field. This is one area where emerging new evidence may require a medical reversal [26].

11.2 Conclusion

Oncoplastic and breast reconstructive surgery takes time to deliver, is expensive to the health system, and lacks empirical proof of benefit to patients. This type of surgery is an anomaly amongst other breast cancer treatments that normally have been tested in randomised clinical trials. Given the recent evidence, in the least, immediate reconstruction, therapeutic mammoplasty, or contralateral 'symmetrisation procedures' can no longer be put forward to patients as a 'standard' treatment but as an option discussed along with the above evidence and concerns about their oncologic safety. The access to and the proportion of patients undergoing immediate (or delayed) breast reconstruction or oncoplastic surgery, should not be used as a measure of quality of a breast service, when there are legitimate doubts about the safety of such procedures. It is now an ethical imperative that these procedures should be subjected to testing in well-designed randomised clinical trials. Such trials may be difficult to set up and perform, but randomisation has always been difficult in surgical trials. In this case, such difficulty could be overcome by an honest appreciation of the current lack of knowledge about oncological impact, or the lack of definite evidence of patient benefit from reconstructive/oncoplastic procedures. Achieving an equipoise is the important first step in that direction.

Most importantly, the popular use of more extensive local surgery appears to have given us an insight into the natural history of cancer—when surgical trauma exceeds its therapeutic value it may be detrimental to outcome—a phenomenon that may open up peri-operative strategies that could be designed to improve outcomes from cancer.

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