

Overview

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Since the publication of the last edition of this textbook, the field of genitourinary oncology has continued to change dramatically. It has truly become a field that is intensely multidisciplinary, and radiation oncologists, often substantially outnumbered in the multidisciplinary clinic, must be masters of the published data. Genitourinary oncology has become one of the areas in which practicing radiation oncologists are likely to spend a substantial proportion of their time and one that they cannot choose to ignore.

Developments in genitourinary oncology illustrate the best and some of the more problematic aspects of contemporary medicine. There is much research in areas of spectacular technologic advance, but too much has been widely adopted without sufficient and rigorous scientific evaluation. New drug therapies are being rapidly added to practice but how best to incorporate them with existing therapies and radiation remains an urgent need. Randomized trials are being performed, but they often struggle to overcome decades of therapeutic prejudice. This overview provides highlights of the field that are reviewed in greater detail by the authors of the following chapters.

PROSTATE CANCER

Prostate cancer, along with breast and lung cancers, continues to be the most common type of cancer seen by practicing radiation oncologists. This situation reflects the explosion in early case detection through the widespread use of the prostate-specific antigen (PSA) blood test and the successes of therapy. The incidence peaked in the early 1990s, a few years after the introduction of PSA because the prevalence of the disease in the previously unscreened population was reduced. As predicted, the rate fell, but never to baseline levels. It now holds steady at more than twice the original annual incidence, and the detection rates far exceed the death rates.

It is becoming clear that prostate cancer is being detected in many more men than require treatment.¹ Because we still struggle to sort the “tigers” from the “pussycats,” radiation oncologists and urologists have been erring on the side of caution and treating most patients who are diagnosed with prostate cancer.² This will change in the near future because of widely expressed concerns by patients, physicians, and policy makers about overtreatment to the point that prostate cancer has come to be regarded as the “bad boy” of the U.S. healthcare system. Randomized trials are being published that call into question many of our assumptions of the last 30 years.

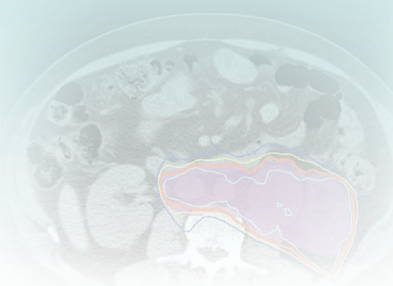
In the years ahead, biomarkers and radiologic advances will likely evolve that, combined with PSA testing and Gleason grading, will be able to determine who does and who does not require treatment. When that happens, the caseload will

decline, and oncologists will be able to concentrate their energies and their effective therapies on the patients who need them. Active surveillance for low-risk prostate cancer is now a mainstream approach that is gathering advocates. What the role of radiation oncologists will be in following these patients is yet to be determined and will, in part, define the way we practice in the future. Will this role default to us, to the urologists, or back to primary care? More than one third of patients who elect for active surveillance end up requiring therapy and many of these, being older patients, choose radiation. Thus, it is incumbent on radiation oncologists to remain involved.

Whether patients require treatment at the time of diagnosis or at some later stage one question that remains central is: Which is the most effective therapy? External beam radiation therapy (EBRT) has progressed substantially over the last two decades. In 1999, the Patterns of Care Study showed that most radiation oncologists in the United States were using three-dimensional conformal techniques. These, in turn, have been replaced by other forms of EBRT, such as intensity-modulated radiation therapy (IMRT), and more recently, by proton beam and stereotactic techniques.

Prospective trials have shown that increased radiation doses yield higher cure rates and that highly conformal techniques are the only safe ways to give these doses.^{3,4} This is a superb example of practice changing on the basis of strong evidence. Whether the more recent evolutions in delivery systems offer dosimetric gains that are of significance remains controversial, but the now-routine use of patient-reported outcomes in radiation therapy trials will answer the question. The use of image guidance has gained widespread acceptance, and few centers currently deliver prostate treatment without it. The next decade will be spent evaluating the patient-reported benefits of these technical advances and integrating them with advances in anatomic and functional imaging to develop boost techniques for subtotal prostate irradiation.

The substantial technical improvements have made EBRT a much more lengthy and expensive process. As a result, alternative approaches have been proposed in an attempt to reduce the social and economic burdens. One such method is hypofractionation. In the past, proponents of its use were considered “heretics,” but evidence now suggests that hypofractionation may be beneficial because prostate cancer may have a low α/β ratio.⁵ Better targeting may now even allow for extreme, and thus patient friendly forms of hypofractionation. These concepts are being tested in randomized trials in the United States, Canada, and Europe. Such investigations are vital because many centers are using this approach without a clear understanding of its biologic implications and risks. Uncertainties remain about the most appropriate doses particularly at the extremes of hypofractionation. Also popular



has been low-dose-rate and high-dose-rate (HDR) brachytherapy, which have many proponents and a body of favorable evidence. Despite this, these therapies are sliding out of favor in competition with other novel radiation and nonradiation approaches.

Patients with early prostate cancer have a disease that is so likely to be cured that quality-of-life issues become important for survivors. Appropriate instruments are being used to report on such issues at an increasing rate, and it is evident that effects on quality of life will become one of the important factors influencing patients and physicians in choosing therapy in the years ahead.⁶

For locally advanced disease, there have been tremendous efforts by the large U.S. and European cooperative groups to perform trials, answer questions, and determine standards of practice. The role of androgen therapy combined with EBRT has become better defined. Results with radiation alone for low-risk disease are sufficiently good that these patients probably do not need androgen therapy⁷; intermediate-risk disease probably does require androgen therapy but only a short neoadjuvant course^{7,8}; and high-risk prostate cancer certainly needs it for years in a manner akin to breast cancer.^{8,9} The role of pelvic lymph node irradiation in locally advanced disease is one that will not go away. RTOG 94-13 has suggested that there may be a small disease-specific survival advantage when it is given, and newer technology is being used to treat the lymph nodes in a fashion that results in less severe side effects than in the past.¹⁰ Active trials are addressing the use of high-dose irradiation in addition to androgen deprivation, and now with novel forms of androgen deprivation also chemotherapy. These represent a brave new frontier in the management of men with a disease that indisputably needs more effective therapy.

Despite the now stable incidence of prostate cancer and the increase in active surveillance the number of patients managed surgically continues to increase, in large part, riding a wave of enthusiasm for robotic technology. A significant proportion of these patients experience a subsequent failure and postoperative radiation is now a large part of the contemporary radiation oncologist's practice. Large randomized trials have clearly shown that irradiation has a role in the postoperative management of prostate cancer. It is becoming widely accepted not only in salvage treatment but also in adjuvant treatment.^{11,12}

Prostate cancer now joins breast and testicular cancers and lymphoma as an exemplary field for clinical research. One trial builds on the "shoulders" of the next, and piece-by-piece, knowledge is accumulated to create a clearer picture of management. Prostate cancer also has become a model in its multidisciplinary approach. Through brachytherapy and combined-modality treatment, radiation oncologists, urologists, and medical oncologists have developed a new and productive spirit of cooperation.

BLADDER CANCER

Bladder cancer is a disease for which substantial gains have been made. A growing body of supportive evidence has made the multimodality approach to bladder preservation a recognized alternative to radical cystectomy.¹³ The Radiation Therapy Oncology Group (RTOG) continues to refine treatment techniques in a series of trials optimizing the doses of irradiation and chemotherapeutic agents. In the United Kingdom and northern Europe, there has been much work on better defining the treatment volume, and randomized trials are answering questions about nodal treatment and the value of whole bladder versus partial bladder irradiation. There is interest in daily image guidance for this highly mobile tumor because the most severe side effects of bladder cancer treatment are

gastrointestinal rather than genitourinary complications. Any method radiation oncologists can find to tighten target volumes and reduce the volume of small bowel treated will be a step forward for patients with bladder cancer. Several new studies look at improving the tolerance of chemoradiation through altered fractionation and gentler chemotherapy.

Several molecular markers and potential molecular targets have emerged in bladder cancer and are creating new avenues for clinical research. Future trial group research will likely be focused on using markers to better select patients for bladder preservation and on the interaction of targeted therapies with chemoradiation.

With all the progress, why is multimodality treatment with organ conservation not more popular with patients and urologists? The urologists have traditionally been the gatekeepers, and their belief that the bladder must be removed rapidly to maximize the chance for cure is strong, as is the belief that an irradiated bladder functions poorly and that superficial and invasive local failures are common and difficult to manage. The section of this chapter on bladder cancer summarizes the data that may be used by radiation and medical oncologists to argue for organ conservation as an alternative to immediate cystectomy for the willing patient. Recent high-profile randomized trials from the United Kingdom and the United States looking at radiation therapy with and without chemotherapy will likely strengthen the argument of those proposing organ preservation.^{14,15}

TESTICULAR CANCER

Seminoma is one of the most radiation sensitive of all tumors, and radiation oncologists take particular pride in being able to promise a high probability of cure. There are few cancers for which cure rates exceed 95%, as they do in stage I to II seminoma. For 40 years, adjuvant irradiation has been the principal player alongside orchiectomy, but more recently, there has been a stepwise retreat in its use. Large volume irradiation has a long-term legacy in the treatment of young male patients. Long ago, the mediastinal field was dropped because of concerns about cardiac toxicity and because improved chemotherapy offered effective salvage in cases in which it was needed. Recent concerns revolve around radiation-induced tumors.¹⁶ Conformal techniques are now routinely used to spare some normal tissue, and in a series of British and Canadian randomized trials, substantial reductions in target volume and dose have been tested and validated.

Since the first edition of this book appeared, the standard adjuvant treatment in Europe has shrunk from a full "dog-leg" field treated to 30 Gy down to a paraaortic field alone treated to only 20 Gy.¹⁷ Trials have looked at single-agent carboplatin as an alternative to irradiation, and it has been found to be effective, although its long-term effects are unknown.¹⁸ In Canada, recognizing that most men with small tumors were disease free after orchiectomy, a policy of surveillance became commonplace, with treatment deferred and given only to those who ultimately prove to have stage II disease. In Chapter 55, Warde documents these changes and the discussions that the contemporary radiation oncologist must have with any newly diagnosed patient. The recent story of irradiation in seminoma mirrors that of irradiation in Hodgkin's disease in that the search for the dose that is "as low as we can go" has been driven by the success of the treatment.

KIDNEY AND URETERAL CANCERS

Renal cancer, cancer of the renal pelvis, and cancer of the ureter have traditionally been the preserve of the surgeon.

There has been a tremendous stage shift in renal cancer with the routine discovery of small, incidental tumors on abdominal computed tomography (CT) scans performed for other reasons. Development of partial nephrectomy, laparoscopic nephrectomy, and percutaneous ultrasound ablation has provided effective therapy that cannot be matched by any medical or radiation therapy alternative.

Although renal cell cancer is recognized to be relatively insensitive to radiation, irradiation has a role to play in locally advanced or metastatic disease. It may be considered as an option after resection of disease with positive margins or after resection of an isolated local recurrence. Intraoperative irradiation may be used as a supplement to EBRT to deliver the high doses required for local tumor control without causing excessive bowel toxicity. In metastatic disease, irradiation to a high dose has an important role in maintaining the quality of life of patients who may live for many years. Stereotactic irradiation has become commonplace for the treatment of brain metastases, and this technique allows for the delivery of the high doses needed to ablate disease in this common site of spread. Because patients are now living longer with the development of effective targeted agents, it is likely that these techniques will be in high demand for the management of metastases outside the central nervous system (CNS).

Cancers of the renal pelvis and ureter are different from renal cell adenocarcinomas. Because they are transitional cell in origin, they behave more like bladder cancer and are more sensitive to irradiation and cisplatin-based chemotherapy. Organ-sparing approaches are not used, however. There is little gain in function or quality of life for preserving a kidney or ureter when another exists, and surgery is the mainstay of treatment. Chemoradiation may offer some assistance when the disease is locally advanced or has spread to nearby lymph nodes.

PENILE CANCER

Penile carcinoma is another cancer for which organ conservation may be expected to be popular. In Chapter 57, Crook and Mazeron demonstrate that penile cancer may in many ways be regarded like any other skin cancer but in one way it stands apart, and that is in its high propensity for nodal spread. They also show that effective organ-sparing radiation treatment is possible. Treatment is technically challenging, and in the United States, where men are circumcised and the disease is rare, there is little accumulated experience. However, treatment by brachytherapy or EBRT follows simple first principles, and it is not beyond the reach of any skillful radiation oncologist.

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