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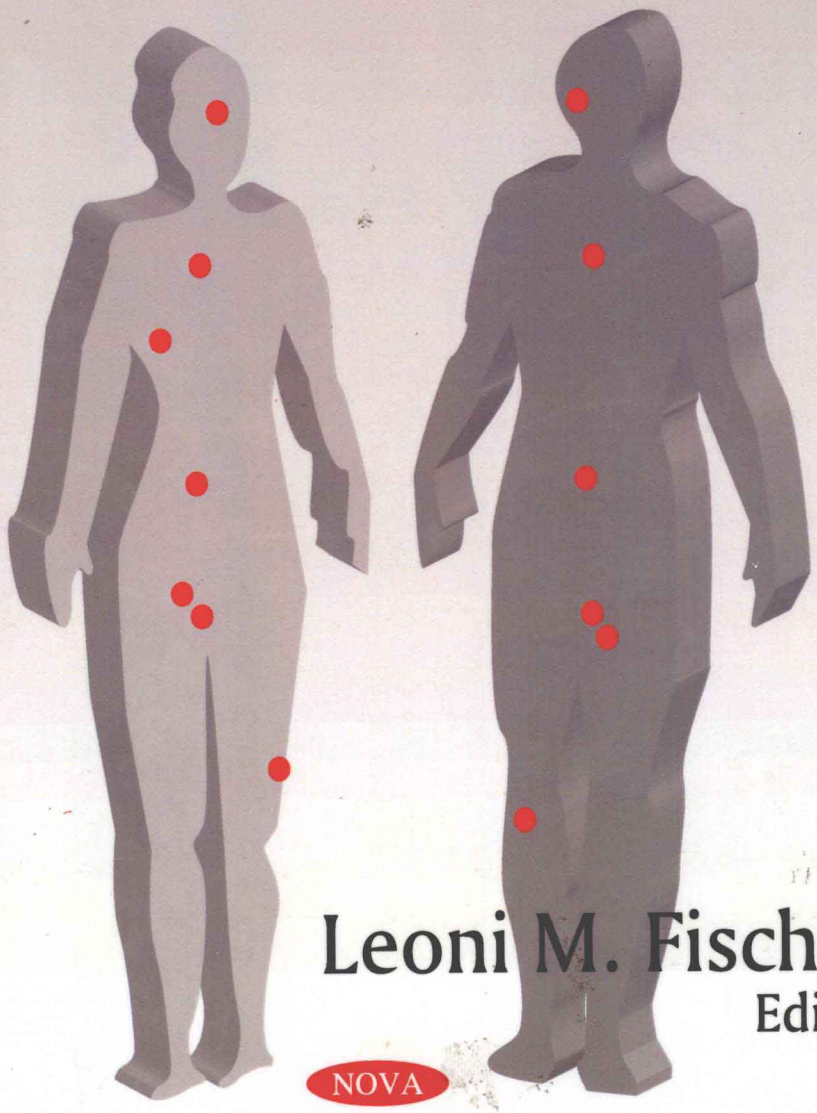
BRACHYTHERAPY

Types, Dosing and Side Effects



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CANCER ETIOLOGY, DIAGNOSIS AND TREATMENTS

BRACHYTHERAPY: TYPES, DOSING AND SIDE EFFECTS

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Preface

Brachytherapy, also known as internal radiotherapy, is a form of radiotherapy where a radiation source is placed inside or next to the area requiring treatment. Brachytherapy is commonly used as an effective treatment for cervical, prostate, breast, and skin cancer and can also be used to treat tumours in many other body sites. Brachytherapy can be used alone or in combination with other therapies such as surgery and chemotherapy. This book presents current research from around the globe in the study of brachytherapy including High Dose Rate (HDR) Intracavitary Brachytherapy for cervical, breast and prostate cancer, as well as nanobrachytherapy and Brachytherapy for soft tissue sarcomas.

Chapter 1 - The increasingly routine use of prostate surface antigen (PSA)-based screening has led to the diagnosis of more patients with organ-confined prostate cancer. These localized cancers are routinely treated with radical prostatectomy, external beam radiation therapy or prostate brachytherapy. Prostate brachytherapy is an appealing treatment for reasons including patient convenience, a favorable toxicity profile and cost-effectiveness. Consequently, the utilization of brachytherapy is increasing, both in the United States and around the world. Although there are no randomized trials comparing the various treatment modalities, and long-term efficacy data are somewhat limited, the available evidence suggests that prostate brachytherapy achieves favorable results in lower risk patients that rivals those achieved with radical prostatectomy and external beam radiation therapy in terms of local control, prevention of biochemical relapse, and prevention of prostate cancer specific and overall mortality. As improved risk stratification and imaging modalities increase the accuracy with which patients with organ-confined disease can be identified, these results can be expected to improve. In addition to better patient selection, ensuring the proper dose is delivered also impacts the efficacy of treatment. Improved techniques such as three-dimensional intra-operative planning can increase the likelihood that a sufficient and homogenous dose is delivered to the entire prostate including all suspicious or known lesions identified by clinical exam, imaging and prostate biopsy. In part due to these diagnostic and technical advancements, prostate brachytherapy may be an effective treatment for localized intermediate-risk disease, both as monotherapy and in combination with external beam radiation therapy.

Chapter 2 - Purpose: To evaluate the outcomes, toxicities and dose-volume histogram (DVH) parameters of high-dose-rate interstitial brachytherapy (HDR-ISBT) in the management of primary and recurrent gynaecologic malignancies.

Materials and Methods: Between 2001 and 2009, 38 patients with gynaecologic cancer were treated at L'Hotel-Dieu de Quebec with Ir-192 remote afterloading HDR-ISBT, using a Syed-Neblett template for implant technique and inverse planning simulated annealing (IPSA) algorithm for dosimetry optimization. The median HDR-ISBT dose delivered was 30Gy (range: 18–35), given in 4–6 Gy/fraction. All patients received pelvic external beam radiation therapy (EBRT). Four patients with vaginal recurrence (R) also had previous intracavitary brachytherapy (ICBT). Toxicities were assessed according to CTCAE v3.0. Total equivalent dose in 2-Gy fractions (EQD2) was calculated, combining HDR-ISBT and EBRT contributions. Results were compared with published data.

Results: Of the 38 patients reviewed, 30 were treated for primary malignancies (PM) of the vagina (n=15), cervix (n=9), vulva (n=2) or Bartholin's gland (n=4) and 8 had recurrent gynaecologic cancer. FIGO stage distribution for PM was: I (n=2), II (n=12), III (n=13), IV (n=3). Median age was 57. Median follow-up was 20.6 months (range: 1-92). Complete response rate (CR) was 82% for PM versus 75% for R. Local control (LC) for PM and R was 86.7 vs 37.5% at 2 years and 81.3 vs. 37.5% at 5 years (p=0.007). 5-year overall survival was 78.9 vs 14.3% (p<0.001). DVH parameters for target volume showed a median V100 of 97.5% and EQD2 D90 and D100 of 89Gy10 and 69Gy10. For OAR, median dose to 2cc (D2cc) was 80.1Gy3 for rectum and 76.9Gy3 for bladder. These DVH values appear to be at least equivalent to those published for MRI guided ICBT following the GEC-ESTRO recommendations, except for our rectal D2cc that was higher. The median D0.1cc for urethra was 79.7Gy3. Twelve patients experienced grade 3-4 late toxicities (gastrointestinal and genitourinary) but only two of them were still suffering from grade 3-4 toxicity at last follow-up.

Conclusion: The use of HDR-ISBT offers good long-term LC, especially in PM, at a cost of possible transitory severe late toxicities. This therapeutic option should be considered for PM that cannot be optimally treated with ICBT and for isolated R. DVH parameters of OARs recommended by the Gyn GEC-ESTRO and urethral D0.1cc or D10 should be reported. Further investigations are needed to define dose-volume constraints in HDR-ISBT.

Chapter 3 - High-dose-rate (HDR) intracavitary brachytherapy (ICBT) is widely applied for patients with cervical cancer. The advantages of HDR-ICBT are time and resource conservation, outpatient service, convenience, and optimal cost-effectiveness. Meta-analysis shows similar local control and complications in comparison with low dose rate ICBT. The rectum is the most common organ at risk (OAR) in the reports about HDR-ICBT. The International Commission on Radiation Units and Measurements (ICRU) 38 report defined reference points for dosimetry. The rectal complications are related not only to cumulative ICRU doses to the rectum, but also to external parametrial doses (PMD). For diminishing biologically effective dose (BED) of the rectum, rectal balloon inflation, small fraction size of point A, or intensity modulated radiation therapy (IMRT) may be beneficial to patients with potentially high rectal doses. Correlations between dosimetry and complications of the urinary bladder and sigmoid colon are controversial due to organ movement. CT/MRI-based treatment planning is suggested for more accurate dosimetry because doses of ICRU reference points are typically underestimated using orthogonal radiography-based dosimetry. To improve local control rate, MRI-guided brachytherapy is preferred for better target delineation and dose coverage. The unsolved issues of HDR-ICBT are weighting relative to external beam radiation therapy, dose rate effect, impact of concurrent chemotherapy, optimal dose-fraction, interfractional dose variation, brachytherapy devices, dosimetry using 3D

planning, and reference points/volume for OAR. This chapter presents a comprehensive literature review and discussion.

Chapter 4 - In the present paper a therapeutic option for the treatment of Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) is described. It basically consists in a superficial high dose brachytherapy, characterized by the use of a ready-to-use kit, in which a radioactive beta-emitting isotope, incorporated in a specially formulated inert, synthetic resin, is applied on the surface of BCC and SCC tumours. When the product is applied on the lesion, a beta emitter brachytherapy irradiation is performed, strictly limited to the area and depth affected by the tumour invasion. The electrons from high energy (> 1MeV) beta emitters isotopes deposit more than 90 % of the dose to the first two mm of the skin, which is the depth usually interested from tumour invasion, but spare the deeper tissues from irradiation. The therapy has been used in a large variety of BCC and SCC: tumours of very large sizes, relapsing or recurrent forms, multifocal lesions, without restriction of site, dimension, clinical or histological type, patients clinical situation, with exclusion of the lynphonode metastatic forms. More than 1200 lesions on 370 patients, with histologically, dermoscopically, or clinically confirmed diagnosis of BCC and SCC, have been treated. After a follow up of 12 - 78 months, a complete response was obtained in 98% of the treated lesions, in 89 % of the lesions after a single application, while in 11% of the patients two or three treatments were performed. A clear advantage of the proposed treatment respect to the surgery is especially evident for all the tumours located in difficult sites, on which surgery would be difficult (nose, ears, eyelids, etc.). The technique should be, in our opinion, the first choice treatment in all those patients with a high number of lesions, or with tumour relapses, in those with tumours located in particular sites, where surgery would produce functional mutilations (penis, vulva, eyelids etc.) and, finally, in older, infirm, or otherwise inoperable ones.

Chapter 5 - Breast cancer treatment has changed substantially in the past several decades. Initially, all women were treatment with mastectomy. However, this is a major and often a very difficult surgery for the patient, both physically and emotionally. Several studies were published that demonstrated acceptable local control and equivalent survival when mastectomy was compared with whole breast irradiation (WBI) following the surgical removal of the tumor[1,2]. This shifted the treatment paradigm as the new standard of care became 5 – 6 weeks of radiation delivered to the whole breast. Although a survival benefit for WBI has not been demonstrated in prospective, randomized trials, a metaanalysis suggests that there may be a small benefit for women less than 60 years of age [3].

Chapter 6 - Introduction

The use of balloon brachytherapy devices for High Dose Rate (HDR) partial breast irradiation is well established. Alternatively, balloon applicators can be used for HDR brachytherapy treatment of gynecological malignancies. This includes treatment for (1) post operative endometrial cancer and (2) inoperable endometrial cancer. Here, we describe the clinical and dosimetric methodology for these two treatment sites.

Materials and Methods

Balloon devices were used as applicators for vaginal vault irradiation for patients treated post-operatively and for treatment of the uterus for those with inoperable endometrial cancer. Patients were treated with a Varian iX Ir-192 high dose rate brachytherapy source. Three dimensional treatment planning was done with BrachyVision 8.2 and was based on CT scans acquired for each treatment fraction.

Results

For irradiation of the vaginal vault, the use of a balloon applicator reduces the frequency of air gaps between the vaginal mucosa and the applicator as compared to a standard segmented cylinder applicator. It provides excellent radiation dose coverage of the target area with acceptable doses to the bladder and the rectum. For treatment of the uterine serosa, the dose distribution is similar to that obtained through the use of Simon-Heyman capsules while maintaining the ease of a single-entry applicator. It also provides a more reproducible treatment because the volume of the balloon is easily duplicated from fraction to fraction. The insertion and removal of the applicator in both treatment sites is well tolerated.

Conclusion

The use of balloon applicators in gynecological sites is a clinically feasible and safe method of patient treatment. Balloon applicators offer the simplicity of a single-entry, single channel tool. The applicator itself is patient specific based on the fill volume of the balloon and can be the same from fraction to fraction, or can adapt if the patient anatomy changes. The dose distributions obtained are similar to conventional treatment devices. Other treatment sites may also benefit from the use of a balloon applicator.

Chapter 7 - Brachytherapy is an important cancer therapy modality. The common cancers for which this kind of therapy is useful include skin cancer, prostate cancer, cervical cancer,etc. This kind of treatment has been used in Thailand for a long time, and many reports on this cancer treatment have been done there. In this specific article, the author summarizes the important reports on brachytherapy in Thailand. Special focus is placed on types, dosing and side effects.

Chapter 8 - Nanomedicine has become the new emerging medical science. It can be applied to many branches of medicine. Application of nanomedicineto cancer therapy can be seen, and nanobrachytherapy is the newest approach for brachytherapy. This article will briefly discuss this new approach of brachytherapy.

Chapter 9 - Introduction

Limb-sparing surgery and adjuvant radiation have replaced amputation as the mainstay treatment for patients with soft tissue sarcoma (STS) of the extremity, since adjuvant radiotherapy has been shown to improve local control and disease-specific mortality. Additional brachytherapy, interstitial tumor bed irradiation, following conservative surgery represents a means of enhancing the therapeutic ratio, as biological and dosimetric advantage over external beam radiotherapy (EBRT).

Success in the management of STS is often limited by the extension of lesions to neurovascular structures. In an effort to preserve limbs, conservative surgery with adjuvant high-dose-rate (HDR) brachytherapy has been reported, whereas little is known about the tolerance of peripheral nerves to brachytherapy. The purpose of this study was to determine the oncological outcome in patients with STS treated with adjuvant HDR brachytherapy and to evaluate the efficacy and radiation neurotoxicity of HDR brachytherapy in patients with STS in contact with neurovascular bundles.

Methods

Between 1995 and 2000, 28 patients with 29 STS of the extremity and superficial trunk were treated in our institute with limb salvage surgery followed by fractionated HDR brachytherapy. Seven of the 28 cases involved the neurovascular bundle. Afterloading catheters placed within the tumor bed directly upon the preserved neurovascular structures were postoperatively loaded with Iridium-192 with a total dose of 50 Gy. To further

investigate the subclinical nerve damage by HDR brachytherapy, motor nerve conduction velocity studies were carried out in 3 patients.

Results

There was one local recurrence and 8 lung metastases. Eighteen patients survived and continued to be disease-free. One patient died of heart problems. With a median follow-up period of 34 months, the 5-year actuarial overall survival and disease-free survival rates were 68.1 and 51.9%, respectively. Complications included 4 wound complications, 2 nerve damage, and one bone fracture. But there was no practical and electrophysiological finding of neurotoxicity due to HDR brachytherapy.

Discussion

This study demonstrated that conservative surgery combined with adjuvant HDR brachytherapy is the treatment of choice for patients with STS to avoid amputation or major limb function loss. Several large clinical studies have established the efficacy of conventional low-dose-rate brachytherapy as an adjuvant therapy for STS. The use of HDR is considered to be an attractive alternative, because this technique allows treatment to be given in minutes instead of days. Here, we discuss the effectiveness and complications of brachytherapy in STS, with a review of the pertinent literature.

Chapter 10 - Introduction

Gallbladder carcinoma has an extremely bad prognosis. The radical surgery is acceptable for minority of patients; external radiotherapy or chemotherapy is ineffective. The aim of study was to evaluate the therapeutic effect of a combination of intraluminal brachytherapy (ILBT) and metallic stent implantation in the treatment of patients with nonresectable biliary tumours.

Patients and Methods

43 patients aged 41-80 years with nonresectable biliary malignancies - gallbladder carcinoma (n=14), Klatskin´s tumour (n=25) and carcinoma of papilla Vateri (n=4) were treated with a combination of ILBT (Ir 192, high dose radiation, total dose 30 Gy) and metallic stent implantation (ELLA CS®). ILBT and stent insertion were performed through percutaneous drainage in all patients.

Results

The mean survival in patients with gallbladder carcinoma was 219 days (range 86-609, median 190 days) in patients with Klatskin´s tumour 483 days (range 85-1223, median 436 days) and in patients with carcinoma of papilla Vateri 850 days (range 48-1518, median 917 days). The rate of 2-year survival in these groups was 0%, 20% and 50% respectively. The survival time differed significantly. The mean time of stent patency was 203, 434 and 850 days respectively. No complications related directly to ILBT were observed.

Conclusion

ILBT combined with percutaneous stent implantation is a safe method and appears to prolong survival in inoperable patients with Klatskin´s tumour and carcinoma of papilla Vateri. No similar effect was observed in patients with gallbladder carcinoma.

Key Words: Gallbladder carcinoma, biliary tumours, percutaneous biliary drainage, selfexpandable stent, intraluminal brachytherapy

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Chapter 1

The Efficacy of Modern Prostate LDR Brachytherapy as Monotherapy and Options for Salvage

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The increasingly routine use of prostate surface antigen (PSA)-based screening has led to the diagnosis of more patients with organ-confined prostate cancer. These localized cancers are routinely treated with radical prostatectomy, external beam radiation therapy or prostate brachytherapy. Prostate brachytherapy is an appealing treatment for reasons including patient convenience, a favorable toxicity profile and cost-effectiveness. Consequently, the utilization of brachytherapy is increasing, both in the United States and around the world. Although there are no randomized trials comparing the various treatment modalities, and long-term efficacy data are somewhat limited, the available evidence suggests that prostate brachytherapy achieves favorable results in lower risk patients that rivals those achieved with radical prostatectomy and external beam radiation therapy in terms of local control, prevention of biochemical relapse, and prevention of prostate cancer specific and overall mortality. As improved risk stratification and imaging modalities increase the accuracy with which patients with organ-confined disease can be identified, these results can be expected to improve. In addition to better patient selection, ensuring the proper dose is delivered also impacts the efficacy of treatment. Improved techniques such as three-dimensional intra-operative planning can increase the likelihood that a sufficient and homogenous dose is delivered to the entire prostate including all suspicious or known lesions identified by clinical exam, imaging and prostate biopsy. In part due to these diagnostic and technical advancements, prostate brachytherapy may be an effective treatment for localized intermediate-risk disease, both as monotherapy and in combination with external beam radiation therapy.

Although of concern, local recurrences after properly performed and adequately dosed prostate brachytherapy are rare. Salvage options for these local recurrences exist and include

prostatectomy, repeat focal brachytherapy, cryotherapy and high frequency ultrasound (HIFU). The infrequency of local recurrences limits the experience with and the evaluation of these salvage modalities, but more recent series have demonstrated reduced toxicity rates and a significant percentage of patients with durable responses.

In conclusion, adequately dosed prostate brachytherapy has demonstrated efficacy in treating organ-localized prostate cancer. Ultimately, due to the indolent nature of many prostate cancers, even longer term follow up will be needed to further assess the technological advances that can be expected to improve patient selection, dose delivery and salvage treatments.

Introduction

The number of men who undergo prostate-specific antigen (PSA)-based screening for prostate cancer has dramatically increased since the late 1980s, increasing over twelve-fold from 1988 to 1991 [Potosky, Miller et al. 1995]. Subsequently, the proportion of patients diagnosed with early stage disease has increased. Recent data suggest that currently more than 60% of patients with prostate cancer are diagnosed with non-palpable disease, and almost half have disease that can be classified as low-risk [Partin, Mangold et al. 2001; Cooperberg, Moul et al. 2005]. Many of these patients have disease confined to within the prostate and are, therefore, candidates for targeted local therapy. Conventional treatments for organ-confined prostate cancer are radical prostatectomy or radiation therapy, delivered either using external beam radiation or interstitial brachytherapy. Although there have been no modern randomized controlled trials comparing surgery to radiation therapy, large series have suggested similar local, distant and overall prostate cancer control rates with the two treatments [D'Amico, Whittington et al. 1998].

Brachytherapy has been used to treat prostate cancer dating back to the early 1900s, when radium treatments were delivered using a transurethral catheter by Pasteau and Degrais [Bagshaw, Kaplan et al. 1993]. Early transperineal implants also used radium and were described starting in 1915 by Benjamin Stockwell Barringer at Memorial Hospital [Barringer 1924; Barringer 1938] and by Young and colleagues at Johns Hopkins University in the early 1920s. In the 1950s, Flocks and colleagues at the University of Iowa performed over one hundred gold-198 interstitial implants during open surgery [Holm 1997]. The first iodine-125 implants were reported from Memorial Sloan-Kettering Hospital in 1972 [Whitmore, Hilaris et. al. 1972]. These iodine-125 implants were also performed at the time of open surgery and guided by direct visualization and palpation of the prostate gland without the use of a template. Consequently, an imprecise and non-homogenous dose was delivered to the prostate and the long-term disease control rates of patients treated in this manner were suboptimal.

In the 1980s, Danish physicians developed techniques to plan prostate brachytherapy in advance using ultrasound mapping and templates to guide therapy[Holm 1997]. These innovations made it possible to deliver a more homogenous dose to the entire prostate with increased accuracy using a transperineal approach. Modern prostate brachytherapy has integrated additional techniques including three-dimensional ultrasound guidance of seed deployment, intra-operative planning and dosimetry and, more recently, CT- or MRI-guided radiation planning. Increasing experience with these technologies allows for the targeted

delivery of a high dose of radiation to the prostate gland and small surrounding margin with an increased sparing of adjacent normal tissue, most notably the bladder and bowel.

Table 1. Isotopes commonly used in LDR prostate brachytherapy

	Iodine-125	Palladium-103
Energy	27 keV x-ray	21 keV x-ray
Half-life	59.6 days	17 days
Approximate activity per seed	0.37 - 0.45 mCi	1.3 - 1.5 mCi

Currently, most prostate brachytherapy procedures in the United States are performed on an outpatient basis using permanent interstitial implants inserted through the perineum under general anesthesia. These permanent implants typically consist of small iodine-125 or palladium-103 radioactive seeds that deliver low-dose-rate treatment (LDR) of less than 40 cGy per hour to the prostate over weeks to months (Table 1). High dose rate (HDR) treatments of greater than 1200 cGy per hour have also been increasingly used and usually involve the placement of temporary prostate catheters from which radiation sources can be placed and removed. Consequently, HDR therapy usually requires a short hospitalization as patients receive several treatments over a few days.

Typically, prostate brachytherapy is either delivered as monotherapy or given as a radiation boost after external beam radiation therapy. When used as monotherapy, brachytherapy is most appropriate for patients who have a high probability of organ-localized disease because of the relatively steep dose gradient that exists in the peri-prostatic tissue. Thus, in the past, the limited numbers of patients diagnosed with early stage disease and the absence of accurate risk stratification limited the number of patients that could be identified as good candidates for brachytherapy as monotherapy. PSA-based screening has increased the detection of early stage prostate cancer[Cooperberg, Moul et al. 2005], and refinements in risk stratification based on clinical stage, Gleason score and PSA [Partin, Mangold et al. 2001] have increased the ability to predict organ-confined disease. Additionally, improvements in imaging techniques such as endorectal ultrasound and prostate MRI have further improved patient selection. Recent improvements to prostate MRI in particular have enhanced resolution and increased the sensitivity and specificity with which prostate cancer can be detected [Lawrentschuk and Fleshner 2009].

Prostate brachytherapy is convenient, minimally invasive, and cost effective when compared to the other standard treatments for prostate cancer[Buron, Le Vu et al. 2007]. In contrast to external beam radiation therapy, prostate brachytherapy does not deliver radiation directly through the skin surface, and therefore the doses of radiation delivered to the normal tissues surrounding the prostate can be minimal. Unlike radical prostatectomy, prostate brachytherapy is typically performed as an outpatient procedure and can often be performed on older men with multiple medical comorbitities that would be poor candidates for prostatectomy.

Although a detailed discussion of morbidity following prostate brachytherapy is beyond the scope of this chapter, the toxicity profile of modern prostate brachytherapy is favorable. A recent study utilizing validated patient questionnaires obtained both before and after therapy[Sanda, Dunn et al. 2008] reported that only 1-5% of patients needed prolonged

urinary catheterization after the procedure, with risk directly related to the size of the prostate gland and the degree to which urinary symptoms were present prior to treatment. The risk of erectile dysfunction varied with age, but potency was maintained in a majority of patients (approximately 79%) and erection-enhancing drugs were able to restore potency in the majority of patients (80%) in whom it was diminished after treatment. The rate of significant rectal toxicity was between 0-1%. Although there were inherent differences in patient selection, the toxicities associated with brachytherapy compared well with either radical prostatectomy or external beam radiation therapy.

The increase in eligible patients diagnosed with early-stage prostate cancer and the growing experience of physicians performing prostate brachytherapy has provided the impetus for a dramatic rise in the number of brachytherapy procedures performed in the United States and the rest of the world. In the United States, for example, data from an multi-institutional observational database of men with prostate cancer demonstrate a gradual increase in the percentage of prostate cancer patients treated with prostate brachytherapy from 3.4% to 5.3% from 1989 to 1998, and then a more rapid rise until brachytherapy accounted for the treatment of 13.1% of all patients diagnosed from 1999 to 2001 [Cooperberg, Grossfeld et al. 2003]. The overall use of brachytherapy for any malignancy increased in nineteen European countries by approximately 11% from 1997-2002, with 16% of those patients receiving prostate brachytherapy [Guedea, Ellison et al. 2007]. Japan introduced permanent iodine-125 implants in 2003, and already over 90 institutions have treated over 10,000 patients in this manner [Yoshioka 2009]. Surveys conducted in 1995 and 2000 in Australia and New Zealand demonstrate a significant increase in specialists who recommended prostate brachytherapy for organ-localized disease, although still significantly less than the number of physicians who recommended radical prostatectomy or external beam radiation therapy[Chong, Austen et al. 2006].

As interest in prostate brachytherapy increases, important considerations for both patients and physicians include the efficacy of this procedure and the options for local salvage when necessary.

Efficacy

Prostate cancer is often a slowly progressive disease, and thus it can take years and even decades for treatments to demonstrate a survival benefit [Bill-Axelson, Holmberg et al. 2008]. Consequently, prostate cancer studies often use the surrogate endpoint of biochemical failure (a significant rise in PSA following treatment) as a preliminary means to evaluate and compare the efficacy of potential therapies. Biochemical failure is associated with local failure [Stone, Stock et al. 2007], the development of distant metastases and prostate cancer death [Pound, Partin et al. 1999]. Unfortunately, various definitions of biochemical failure have been used as the sensitivity and experience with PSA testing has increased (Table 2), making it more challenging to compare published studies [Roach, Hanks et al. 2006]. Two common definitions of biochemical failure are generally used, the American Society for Therapeutic Radiation and Oncology (ASTRO) consensus 1997 definition and the ASTRO Phoenix (Nadir + 2 ng/ml) definition, although the ASTRO Phoenix definition is more sensitive and specific [Thames, Kuban et al. 2003]. The increased sensitivity and specificity

of the Phoenix definition has also been confirmed specifically for brachytherapy patients [Kuban, Levy et al. 2006].

No modern prospective randomized trials have directly compared the efficacy of radical prostatectomy, external beam radiation therapy and brachytherapy [D'Amico, Whittington et al. 1998]. Attempts have been made to conduct such trials, for example by the Southwest Oncology Group in the 1980s and a more recently in low-risk prostate cancer patients in Canada, but all have had to close because of poor accrual [Klein, Ciezki et al. 2008]. Consequently, the efficacy of prostate brachytherapy has been estimated using single and multi-institutional series. In some cases, attempts have been made to directly compare efficacy results with prostate cancer patients that have undergone radical prostatectomy or external beam radiation as their primary treatment. However, these comparisons are limited by inherent bias in patient selection, although some studies have endeavored to account for this by comparing the results from equivalently risk-stratified patients.

Current guidelines for the risk stratification of prostate cancer patients categorize patients as low, intermediate and high risk [National Comprehensive Cancer Network 2009]. These risk groups are based on the established risk factors: PSA-level, clinical stage and Gleason score - factors that have been demonstrated to predict for the pathologic extent of disease and for prognosis following treatment [Partin, Mangold et al. 2001]. However, these risk groups are limited in that they do not take other prognostic factors into account: age, medical comorbidities, PSA-velocity, percent positive cores identified at biopsy, presence of perineural invasion, imaging results, among others[D'Amico, Renshaw et al. 2004; D'Amico, Renshaw et al. 2005; Beard, Schultz et al. 2006]. Thus, there is significant heterogeneity within each risk group. Furthermore, the risk groups have changed over time and are not uniform among different centers, limiting the ability to compare between studies (Table 3). Nevertheless, stratifying patients into risk groups based on prognostic factors remains useful when examining efficacy data from published studies.

Improved risk stratification, innovations in brachytherapy technique, increased experience and combined modality therapy are likely to have improved the efficacy of prostate brachytherapy. More sophisticated risk stratification has improved patient selection and allowed for the treatment of particular subgroups of patients that may not have otherwise been eligible. Improved technology has allowed for the delivery of a higher, more homogenous and more accurately targeted radiation dose to be delivered to the prostate. Prostate brachytherapy has also been combined with androgen deprivation therapy and external beam radiation therapy, although combinations with these other treatments make comparisons among previous published series more difficult to interpret (Table 2). Androgen deprivation therapy, in particular, is often given prior to prostate brachytherapy in order to downsize the prostate, although in some series it is has also been used after brachytherapy in intermediate- or high-risk patients.