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Overview

Brachytherapy: Current Status and Future Strategies — Can High Dose Rate Replace Low Dose Rate and External Beam Radiotherapy?

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Abstract

Brachytherapy delivers the most conformal high dose radiotherapy possible to the prostate, using either a low dose rate (LDR) or high dose rate (HDR) technique. It may be used either alone as monotherapy or in combination with external beam radiotherapy (EBRT) as a local boost. Comparative efficacy studies, including one randomised controlled trial, consistently show higher cancer control rates when brachytherapy is used compared with EBRT alone, with even some evidence of improvement in survival. There are now extensive mature data supporting the use of LDR as monotherapy for patients with low-risk and selected intermediate-risk disease, with most series reporting long-term disease control rates of over 90% after high-quality implants. HDR is most commonly combined with EBRT to treat intermediate- and high-risk disease, with disease control rates of over 90% reported. The low alpha/beta ratio of prostate cancer combined and the ability to optimally sculpt dose distribution provides the biological and dosimetric rationale for HDR. HDR enables more consistent implant quality than LDR, with evidence of lower acute and late toxicity. Many dose and fractionation schedules of HDR in combination with EBRT have been investigated, but a single fraction of 10–15 Gy is commonly combined with EBRT to a dose of 40–50 Gy to treat intermediate- and high-risk disease. High disease control rates are also reported with HDR as monotherapy, particularly in patients with low- and intermediate-risk disease. Although older series have delivered four to six fractions of HDR, there is growing evidence to support the delivery of HDR in three or even two fractions. Single-fraction HDR monotherapy is now being investigated and if early data are confirmed with longer follow-up, may well become the treatment of choice for many men with localised prostate cancer.

Key words: Comparative efficacy; external beam; HDR; image guidance; LDR; outcomes

Statement of Search Strategy Used and Sources of Information

Online searches through Pub Med and MedLine were conducted using the search terms ‘brachytherapy’, ‘high dose rate’, ‘prostate cancer’, ‘low dose rate’, ‘SBRT’. Abstracts were reviewed and suitable full-text manuscripts obtained. Priority was given to publications within the past 3 years, with a minimum of 100 patients and a median follow-up of at least 4 years.

Introduction

Prostate brachytherapy enables delivery of an ablative dose of radiation to the cancer with the advantage of rapid fall-off in dose and sparing of neighbouring organs. Modern external beam radiotherapy (EBRT) using inverse planning, intensity modulation and image guidance enables moderate dose escalation, but with a much higher integral dose to the patient, higher cost and greater use of resources [1]. Its use is supported by several randomised clinical trials, which have shown an improvement in biochemical control of about 10% as dose is escalated from around 70 Gy to around 80 Gy [2]. Brachytherapy allows for dose escalation beyond that achievable with EBRT, with a further reduction in dose to the surrounding tissues. Mature data show that brachytherapy results in consistently high local control rates, high disease-free survival and a low risk of long-term morbidity.

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Two types of brachytherapy are commonly used to treat prostate cancer: low dose rate (LDR), involving the permanent implantation of radioactive seeds, and high dose rate (HDR), where the dose is delivered from a single high-activity radioactive source that 'steps' along catheters temporarily implanted into the prostate. Either method delivers a highly conformal dose to the prostate with little dose to surrounding organs. Although there are few randomised trials comparing different methods of radiation delivery, the data strongly suggest that treatment with brachytherapy, alone or combined with EBRT, results in higher disease control rates than achieved with EBRT alone. Grimm and colleagues [3] reported a comparative analysis of prostate-specific antigen survival outcomes on behalf of the Prostate Cancer Results Study Group. A comprehensive literature review was undertaken of studies reporting treatment outcome for localised prostate cancer published between 2000 and 2010. The authors concluded that the highest disease control rates were found with the use of brachytherapy, either alone or combined with EBRT, across all risk groups.

Here we review the current status of prostate brachytherapy, describe emerging trends and address the question of whether HDR can replace LDR and EBRT.

Prostate Brachytherapy: Current Status

Low Dose Rate Brachytherapy

The modern era of prostate brachytherapy began in the mid-1980s with the development of trans-rectal ultrasound (TRUS) to guide the trans-perineal placement of iodine-125 seeds into the prostate [4,5]. Since then, LDR monotherapy has emerged as a standard treatment for men with low- and intermediate-risk disease, with many modern series reporting a biochemical disease-free survival of over 90% [6–18] (Table 1). Disease control rates seem to be higher than those reported with EBRT, even to a dose of 81 Gy [19]. Morris and colleagues [12] recently reported population-based outcomes from British Columbia, Canada. Over 1000 patients were followed for a median of 7.5 years after LDR implant. At 10 years, the biochemical disease-free survival was 94%, and the disease-specific survival was over 99%. Outcome was equally good for both low- and intermediate-risk patients, although the latter were more likely to also have received short-term androgen deprivation therapy around the time of their implant. The only factor associated with the risk of recurrence was implant quality, with a higher rate of recurrence seen in patients with lower dose coverage. Similar high disease control rates have been reported from other single institutions, with a median follow-up of as long as 12 years. A multicentre clinical trial from the Radiation Therapy Oncology Group (RTOG 9805) [17] reported a 92% biochemical disease-free survival after 8 years, with no deaths from disease. With good-quality implants, patients with low-risk disease can expect a long-term disease-free survival in excess of 90% after brachytherapy alone. The reported outcome for patients with intermediate-risk disease is more variable, ranging from 61 to 96%. This may reflect selection factors, use of androgen deprivation or implant quality. Nevertheless it would seem that LDR monotherapy for selected intermediate-risk patients also results in recurrence-free survival in excess of 90%.

Table 1
Biochemical disease-free survival by risk group in series of low dose rate monotherapy

Reference	*n*	Median follow-up (months)	Biochemical disease-free survival by risk group		
			Low	Intermediate	High
[6]	776	54	95%		
[7]	1005	59	72%	74%	58%
[8]	601	69	88%	61%	30%
[9]	463	74	97%	96%	
[10]	768	68	93%		
[11]	706	55	92%	84%	65%
[12]	1005	90	94%	94%	
[13]	273	60	95%		
[14]	1449	82	88%	76%*	62%†
[15]	964	72	88%		
[16]	128	140	86%	80%	62%
[17]	101	97	92%		
[18]	877	49	98%	94%	

* 80% monotherapy.
† 59% monotherapy.

LDR brachytherapy may also be used as a means of local dose escalation in combination with EBRT [20–25] (Table 2). The American Brachytherapy Society (ABS) consensus guidelines favour the use of supplemental EBRT for high-risk patients, and considers it optional for patients with intermediate-risk features [26]. Stone and colleagues [15] reported biochemical disease-free survival at 12 years of 79% for 499 intermediate-risk patients and 67% for 648 men with high-risk disease. Taira and colleagues [23] reported 12 year biochemical disease-free survival of 97 and 91% for intermediate- and high-risk patients, respectively. Supplemental EBRT was delivered to 65% of the intermediate-risk patients and 88% of the high-risk patients, although its use was not associated with risk of recurrence on multivariate analysis. The RTOG 0019 clinical

Table 2
Biochemical disease-free survival by risk group in series of low dose rate combined with external beam radiotherapy

Reference	*n*	Median follow-up (months)	Biochemical disease-free survival by risk group		
			Low	Intermediate	High
[15]	1147	72		79%	67%
[20]	138	92		82%	
[21]	284	94			88%
[22]	1469	72	93%	80%	61%
[23]	473	89			91%
[24]	247	108		93%	
[25]	448	63			86%