BRACHYTHERAPY

Brachytherapy 16 (2017) 1–12

Task Group/Practice Parameter

American Brachytherapy Society Task Group Report: Combination of brachytherapy and external beam radiation for high-risk prostate cancer

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ABSTRACT

PURPOSE: To review outcomes for high-risk prostate cancer treated with combined modality radiation therapy (CMRT) utilizing external beam radiation therapy (EBRT) with a brachytherapy boost.

METHODS AND MATERIALS: The available literature for high-risk prostate cancer treated with combined modality radiation therapy was reviewed and summarized.

RESULTS: At this time, the literature suggests that the majority of high-risk cancers are curable with multimodal treatment. Several large retrospective studies and three prospective randomized trials comparing CMRT to dose-escalated EBRT have demonstrated superior biochemical control with CMRT. Longer followup of the randomized trials will be required to determine if this will translate to a benefit in metastasis-free survival, disease-specific survival, and overall survival. Although greater toxicity has been associated with CMRT compared to EBRT, recent studies suggest that technological advances that allow better definition and sparing of critical adjacent structures as well as increasing experience with brachytherapy have improved implant quality and the toxicity profile of brachytherapy. The role of androgen deprivation therapy is well established in the external beam literature for high-risk disease, but there is controversy regarding the applicability of these data in the setting of dose escalation. At this time, there is not sufficient evidence for the omission of androgen deprivation therapy with dose escalation in this population. Comparisons with surgery remain limited by differences in patient selection, but the evidence would suggest better disease control with CMRT compared to surgery alone.

CONCLUSIONS: Due to a series of technological advances, modern combination series have demonstrated unparalleled rates of disease control in the high-risk population. Given the evidence from recent randomized trials, combination therapy may become the standard of care for high-risk cancers.

Keywords: Prostate cancer therapy; Combination brachytherapy and external beam radiation; High-risk prostate cancer

Introduction

Approximately 225,000 men are diagnosed with prostate cancer in the United States each year, while only 30,000 die from the disease (1). Furthermore, most men die with prostate cancer rather than from the disease (2). These statistics demonstrate that prostate cancer is a heterogeneous disease that can often present as a chronic indolent process, but in a subset of men, it can be a highly

Received 14 June 2016; received in revised form 13 September 2016; accepted 14 September 2016.

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1538-4721/$ - see front matter
http://dx.doi.org/10.1016/j.brachy.2016.09.006

aggressive life-threatening disease. Multiple risk stratification schemas for prostate cancer have been proposed based on various clinicopathologic features including Gleason Score (GS), TNM stage, and baseline prostate-specific antigen (PSA) in an attempt to define distinct prognostic groups of patients to facilitate clinical decision making and research investigation (3–6). The National Comprehensive Cancer Network is one of the most widely used risk classification systems used in the United States and presently divides patients into five risk groups: very low, low, intermediate, high, and very high (3), Based on current clinical practices, the rates of failing definitive therapy are markedly different across risk groups and range from <1% for very low-risk patients to >70% for very high-risk men (7, 8). Furthermore, although the risk of death from prostate cancer is less than 5% for men with very low, low, or select intermediate-risk prostate cancer, greater than 15% of men with high and very high-risk prostate cancer succumb to their disease (7).

Primarily due to the introduction of PSA screening in the early 1990s, there has been a significant downward stage migration for men with prostate cancer. For instance, in 1989, >40% of men diagnosed with prostate cancer were classified as high risk. This is in contrast to 2002 where only 15% of men are classified as high risk (9). However, this stage migration has clearly identified a more biologically aggressive disease that warrants multimodality therapy. There are currently multiple different treatment methods employed in high-risk prostate cancer including surgery alone, external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT), and a combination of external beam radiation, brachytherapy, and ADT. Given that a high number of patients in this category fail treatment and even die of their disease, it is necessary to further improve the treatment strategy for high and very high-risk prostate cancer patients.

Progress in the management of high-risk disease has come from a multifaceted approach, including early diagnosis to identify such cancers at a curable point, imaging for detection of aggressive lesions (10, 11), subclassification of the most lethal forms of high-risk prostate cancer (12–14), improved surgical and radiation techniques (15), earlier introduction of chemotherapy (16), and multidisciplinary coordination of care. Yet perhaps the greatest progress has come from a major conceptual change in treating men with high-risk prostate cancer. High-risk prostate cancer was generally regarded as a disease that by definition harbored micrometastatic disease. This concept drove the search for systemic agents, primarily agents that inhibited androgen receptor signaling, in hopes of treating micrometastatic disease.

ADT by means of surgical or chemical castration has been the most commonly studied form of therapy to treat metastatic disease. It is clear from randomized trials that the addition of ADT to radiotherapy improves outcomes over radiotherapy alone and that the addition of radiotherapy to ADT improves outcomes over ADT alone (17, 18). However, it is unclear if the use of ADT primarily acts to reduce micrometastatic disease or principally to provide radiosensitization to improve local control. It has been demonstrated that ADT inhibits DNA repair and improves the efficacy of radiotherapy *in vitro* by providing a biologically driven form of dose escalation (19, 20). Furthermore, postradiotherapy biopsies from RTOG 9408, a phase III randomized clinical trial comparing radiotherapy to radiotherapy combined with ADT, demonstrated that there was a 50% reduction in biopsy-detected persistent disease locally within the prostate with the addition of ADT (17). This dramatic improvement in local control appeared to translate in a reduction in distant metastases and death from prostate cancer. The incorporation of MRI in prostate cancer staging and treatment planning has allowed

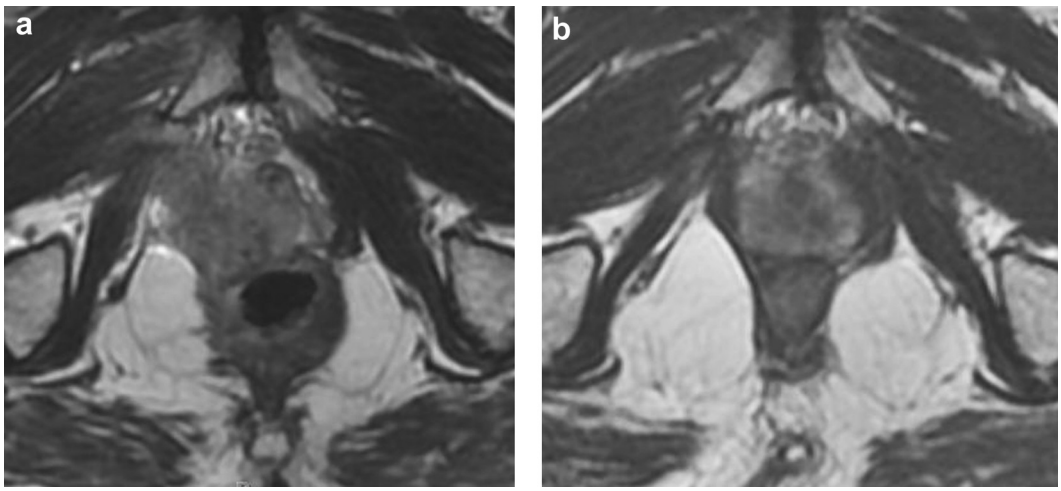

Fig. 1. T2 weighted axial MRI images at the level of the prostate apex demonstrating local effect of ADT. (a) Image taken prior to ADT. (b) Image taken post ADT.

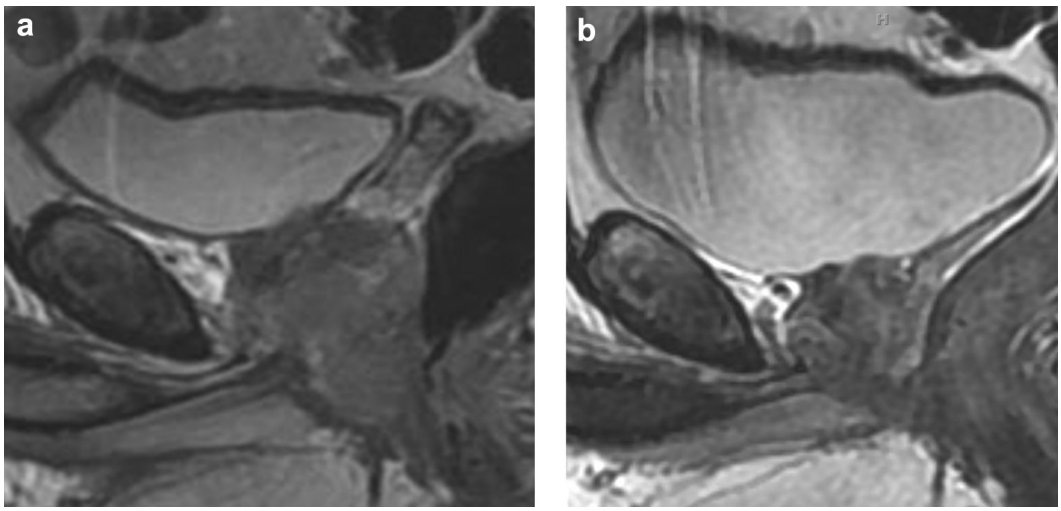

Fig. 2. T2 weighted sagittal MRI images demonstrating local effect of ADT. (a) Image taken prior to ADT demonstrating tumor extension below the penile bulb. (b) Image taken post-ADT demonstrating shrinkage of disease.

radiographic visualization of the impact of ADT on locally advanced disease (Figs. 1–3) (21, 22). These tumor responses further suggest a large proportion of the effect of ADT combined with EBRT is local tumor response. Similarly, men with aggressive local disease who undergo radical prostatectomy followed by further local therapy with adjuvant radiotherapy seem to derive a benefit in progression-free survival, freedom from metastasis, disease-specific survival, and overall survival when local control is established (23). Thus, it is clear that improving local control of prostate cancer translates into improved disease-specific and overall survival in men with high-risk disease. This concept has led many investigators to identify other ways to intensify local therapy with the use of ultra–high-dose escalation to achieve high rates of local control using a combination of external beam radiotherapy and a brachytherapy boost.

In this review, we will summarize recent progress in combined external beam and brachytherapy approaches for high-risk prostate cancer as a powerful form of dose escalation, and the promising long-term outcomes suggesting that CMRT may be the optimal treatment for high-risk prostate cancer.

Data review

This American Brachytherapy Society task group is a collaboration of brachytherapists that was formulated to review and report the technological and clinical evolution of combined modality radiation therapy. We searched PubMed using combinations of the terms: Prostate, High-risk, Brachytherapy, Implant, High-dose-rate, Low-dose-rate, and prostatectomy. In reviewing the development of modern techniques

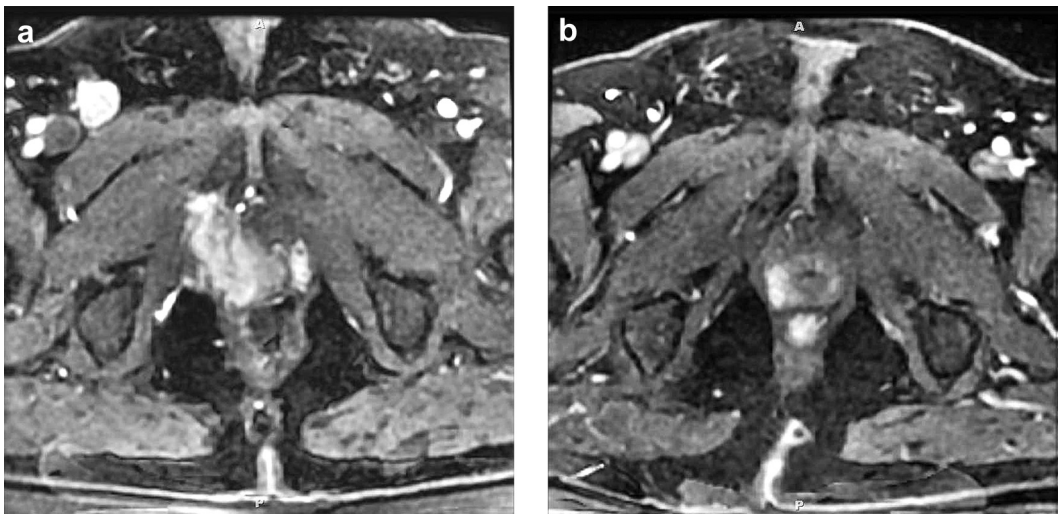

Fig. 3. Dynamic contrast enhanced (DCE) axial MRI images depicting disease infiltrating pelvic muscles prior to ADT (a) and resolution post-ADT (b).

and in reviewing toxicity from CMRT, all applicable manuscripts were reviewed. In evaluating clinical outcomes, manuscripts were restricted to those that reported at least 8-year followup on clinical high-risk patients. High-quality data such as that from prospective randomized controlled trials with shorter followup were included. Manuscripts that did not separate the outcomes for high-risk patients from patients with more favorable disease were excluded. Surgical series that reported outcomes based on pathologic stage and GS as opposed to clinical stage and GS were excluded.

Technical foundation for modern combination therapy

In the late 1980s, ultrasound-guided transperineal brachytherapy replaced open retropubic implant techniques for the insertion of low-dose-rate (LDR) Iodine 125 (^{125}I) seeds. Open implants were pioneered at Memorial Sloan Kettering in the 1970s, but were abandoned primarily because of technical failures. Critz continued open seed implantation, but consistently followed this with external beam radiation therapy (EBRT), making the argument that despite imperfect technique, seed implant provides a tremendous advantage by dose escalation. Critz also insisted on using a very stringent end point of PSA $<$ 0.2 ng/mL, an approach that consistently overestimates clinically significant failure in the short term. However, this allowed direct and competitive comparison with surgical outcomes. When 10-year outcomes were reported in 2004, high-risk patients had a 60% biochemical control rate by this standard. This was a substantial improvement over the best EBRT results of that era, despite the fact that neoadjuvant hormone therapy was not employed (24). A second large report of CMRT from this early era was the 15-year followup data by Blasko *et al.* These results employed a less stringent failure definition of two rises in PSA, yet high-risk results at 15-year followup were in the range of 68% (25). These results were among the most promising radiation reports for high-risk patients at the time and continue to compare favorably to surgical outcomes today.

A major advance in combination therapy was the improvement in imaging and postimplant dosimetry. Early techniques assumed a stable base position, and depth from the grid was used as a surrogate for base depth during needle placement. This resulted in consistent underdosing of the base and inadvertent dose delivery to the genitourinary (GU) diaphragm below the apex. Two-plane ultrasound revolutionized transperineal therapy and allowed direct depth check on sagittal view for all needles. More recently, the adoption of MRI further improved treatment planning and dose delivery. MRI demonstrated profound variation in individual anatomy, discrediting rules of thumb previously employed to define the prostate in relation to adjacent structures. For example, for many years, the penile bulb had been used as a proxy for the prostate apex, given that it is visible on CT. However, MRI has shown that the prostate apex may be 0.5–3.3 cm from the penile bulb. Employing the 1.5-cm rule (apex is 1.5 cm above the penile bulb) resulted in gross underestimation in some and gross overestimation in others (26). MRI also defined critical erectile tissues thought to be responsible for postradiation erectile dysfunction (ED).

Beginning with the pivotal work by Stock (27) and followed by others, a direct tie between brachytherapy quality and outcomes was established (28). Critical in evaluating implant quality was the ability to compare biologically effective doses of brachytherapy with EBRT. Stock *et al.* proposed one of the first models that allowed a meaningful dose response to be assessed in CMRT patients. The biologically effective dose literature has established guideline dose targets in combined implant therapy to achieve optimal cure rates, similar to the earlier D_{90} targets predicting success in monotherapy (29–33). Two schools of thought emerged from this literature. Some have proposed that combination therapy is advantageous for all patients, including those with low-risk disease, to provide further dose escalation. Others have proposed that with optimal implant quality, brachytherapy as monotherapy could be effective in low- and select intermediate-risk patients. There was consensus that high-risk patients require supplemental EBRT to address disease beyond the prostate, including seminal vesicles and potentially pelvic nodal radiation. At this time, it is unclear who benefits from the addition of pelvic nodal irradiation. This question is being addressed in ongoing clinical trials. RTOG 0924 is currently studying the role of pelvic nodal irradiation in high-risk patients in the setting of dose-escalated radiation therapy and ADT and will be valuable in this realm.

A parallel approach to combined modality treatment with EBRT and permanent seed LDR implant was a vast experience with EBRT combined with high-dose-rate (HDR) brachytherapy. A consistent argument in favor of HDR has been improved dose delivery relative to permanent seed implants and improved coverage of seminal vesicle extension commonly encountered in high-risk patients. Radiobiological studies have suggested that prostate cancer may have a low alpha/beta ratio, which would further support the use of high doses per fraction that are feasible with HDR brachytherapy (34). Historically, HDR combination has been associated with a high risk of stricture formation due to high dose per fraction delivered to the urethra and external sphincter (35). However, this was likely due to technical factors including inadequate imaging and catheter displacement between the first and subsequent fractions, suggesting that such complications could potentially be avoided with proper technique. With improving intraoperative imaging techniques allowing for either ultrasound or MRI guidance during implantation, these technical factors are becoming less of a concern (36, 37). Modern series have reported rates of Grade 3

GU toxicity and urinary strictures that are comparable to other modalities (38, 39). Furthermore, there has been a trend toward using fewer, higher dose fractions of HDR brachytherapy for intermediate- and high-risk patients when performed in combination with EBRT, which reduces the risk of dosimetric variability between fractions. Several series have reported the use of two fractions of 8–10 Gy each and have demonstrated 60–90% biochemical control at 5 years in high-risk patients (40–43). However, few studies have reported 10- to 15-year outcomes and long-term data are limited (44). The challenge with evaluating long-term outcomes with HDR combination series is the significant variability in the delivered dose per fraction and total number of fractions used in the published literature over time and across institutions. This is in stark contrast to LDR brachytherapy, where the dose has been relatively constant over decades. These differences in practice patterns have made it difficult to compare the efficacy of HDR and LDR in the setting of high-risk disease with combination therapy. Nonetheless, recent series from institutions with an exceptional commitment to quality suggest high cure rates can be accomplished with excellent quality of life preservation with either treatment approach (40, 45–47). The American Brachytherapy Society has published guidelines with detailed recommendations regarding dose and treatment parameters for both LDR- and HDR-based combination therapy (48, 49).

Combined modality therapy clinical results

Retrospective data

The first reports of excellent disease control in high-risk patients came from a large retrospective series by Merrick (50, 51). A strategy of wide margins and a high-dose implant assured full dose to the prostate. This resulted in success rates up to 88% for high-risk patients with long followup, a success rate comparable to low/intermediate-risk prostate cancer outcomes. Also reported were toxicities such as prolonged dysuria, later determined to be due to inadvertent dose below the prostate (GU diaphragm region). Merrick also demonstrated that critical prognostic factors that have been identified for failure from EBRT alone (T3, >50% positive biopsy, and Gleason pattern 5) did not predict for failure in high-dose external beam plus brachytherapy combination therapy (52, 53). More recently, Bittner *et al.* (54) reported the outcomes of 406 National Comprehensive Cancer Network high-risk patients treated primarily with combination therapy. The patients were stratified into a good prognostic category based on having only one high-risk feature (GS 8–10, PSA > 20, or cT3) and a poor prognostic category based on having a GS 8–10 and one additional risk factor. This stratification was based on an earlier surgical series by Joniau *et al.* that reported a significant difference in prostate cancer–specific survival among these two prognostic groups when the primary treatment was surgery (95% for good prognostic patients vs. 80% for poor prognostic patients, $p = 0.0003$) (55). However, in Bittner's report, with combination therapy, there were no differences in cause-specific survival. Cause-specific survival reached approximately 95% even in the poor prognostic group. These results suggest that with ultra–high-dose escalation, the recurrence rates even for higher risk disease are so low that routine prognostic factors no longer have a significant impact on outcomes in modest sample sizes. Essentially these wide margin studies overcame the dose delivery questions of other series and suggested a large proportion of men with high-risk disease were curable more often than previously realized with sufficient intensive local therapy.

Confirming these results was a combined institution retrospective review of greater than 900 high-risk patients. In this series, Shilkrut *et al.* (56) compared dose-escalated EBRT and ADT results to EBRT plus brachytherapy with ADT and demonstrated a 27% absolute benefit at 8 years followup in terms of biochemical recurrence-free survival (bRFS) with the addition of a brachytherapy boost (87% vs. 60%, $p < 0.0001$). CMRT was also associated with a prostate cancer–specific mortality benefit of 7% (7% vs. 14%, $p = 0.003$). In a pivotal single institution study, Liss *et al.* (57) reported the benefit of combination therapy for patients with Gleason pattern 5 disease, across all outcomes. Gleason pattern 5 has been well documented as one of the strongest prognostic factors for recurrence and metastases after definitive therapy (12, 13, 58). This report demonstrated that with CMRT, there was a substantial benefit in bRFS (89% vs. 65%, $p < 0.05$), freedom from metastases (89% vs. 67%, $p < 0.05$), cancer-specific survival (93% vs. 78%, $p < 0.05$), and overall survival (88% vs. 67%, $p < 0.05$) at just 5 years after treatment (57). Although the overall survival benefit is likely influenced by selection bias in this retrospective study, it is also likely in part, due to the marked benefit in cancer-specific survival. These data show that in high-risk prostate cancer, achieving local control is paramount in achieving long-term disease-free survival. The long-term retrospective high-risk bRFS results of LDR-based CMRT, HDR-based CMRT, external beam alone, and surgery are included in Table 1.

Prospective clinical trial data

The critical question posed by the retrospective studies was whether patient selection accounted for the superior results seen with combination. Three randomized trials have tested whether dose escalation in the form of combination EBRT and a brachytherapy boost improves outcomes over EBRT alone. All three trials have demonstrated improvements in bRFS with the addition of brachytherapy that spans all risk groups of patients (40, 59, 83). The largest and most recently reported trial, ASCENDE-RT, is a prospective randomized trial that accrued 398 patients with

Table 1
Long-term rates of biochemical recurrence-free survival (bRFS) in clinically high-risk patients

Author	Year	*N*	Treatment	% ADT use	bRFS (%)					bRFS definition
					8 yr	9 yr	10 yr	12 yr	16 yr	
Keyes M (59)	2015	139	LDR + EBRT + ADT	100		78				<PSA Nadir + 2
Marshall *et al.* (60)	2014	421	LDR + EBRT + ADT	100				64		<PSA Nadir + 2
Taira *et al.* (53)	2013	329	LDR + EBRT + ADT	73			91			PSA ≤ 0.4
Shilkrut *et al.* (56)	2013	448	LDR + EBRT + ADT	76	87					<PSA Nadir + 2
Fang *et al.* (51)	2011	113	LDR + EBRT + ADT	100			93			PSA ≤ 0.4
Stock *et al.* (58)	2009	181	LDR + EBRT + ADT	100	73					<PSA Nadir + 2
Merrick *et al.* (61)	2011	284	LDR + EBRT ± ADT	63				89		PSA ≤ 0.4
Taira *et al.* (62)	2011	473	LDR + EBRT ± ADT	58				91		PSA ≤ 0.4
Dattoli *et al.* (63)	2010	164	LDR + EBRT ± ADT	Unknown					74	PSA < 0.2 and <PSA nadir + 2
Bittner *et al.* (64)	2008	243	LDR + EBRT ± ADT	60			89			PSA ≤ 0.4
Johnson *et al.* (65)	2015	115	HDR + EBRT + ADT	95			73			<PSA Nadir + 2
Galalae *et al.* (44)	2014	55	HDR + EBRT + ADT	Unknown			69			<PSA Nadir + 2
Prada *et al.* (46)	2012	294	HDR + EBRT + ADT	Unknown			84			<PSA Nadir + 2
Savdie *et al.* (66)	2012	90	HDR + EBRT + ADT	100			54			<PSA Nadir + 2
Krauss *et al.* (67)	2011	96	HDR + EBRT + ADT	100	58					<PSA Nadir + 2
Martinez *et al.* (68)	2016	485	HDR + EBRT ± ADT	70			54			<PSA Nadir + 2
Krauss *et al.* (67)	2011	60	HDR + EBRT	0	58					<PSA Nadir + 2
Demanes *et al.* (45)	2005	47	HDR + EBRT	Unknown			69			<PSA Nadir + 2
Keyes M (59)	2015	137	EBRT + ADT	100		58				<PSA Nadir + 2
Dearnaley *et al.* (69)	2014	422	EBRT + ADT	100			55			PSA < 1.5 × nadir and <2 ng/mL
Shilkrut *et al.* (56)	2013	510	EBRT + ADT	85	60					<PSA Nadir + 2
Stenmark *et al.* (70)	2011	185	EBRT + ADT	100	69					<PSA Nadir + 2
Zelefsky *et al.* (71)	2008	296	EBRT ± ADT	64			37			<PSA Nadir + 2
Stenmark *et al.* (70)	2011	49	EBRT	0	61					<PSA Nadir + 2
Kuban *et al.* (72)	2008	53	EBRT	0	63					<PSA Nadir + 2
Wiegel *et al.* (73)	2014	148	Surgery + adjuvant RT	11			56			PSA ≤ 0.2
Bolla *et al.* (74)	2012	502	Surgery + adjuvant RT	10			61			PSA ≤ 0.2
Swanson *et al.* (75)	2007	122	Surgery + adjuvant RT	9			58			PSA ≤ 0.4
Wiegel *et al.* (73)	2014	159	Surgery	12			35			PSA ≤ 0.2
Bolla *et al.* (74)	2012	503	Surgery	10			41			PSA ≤ 0.2
Swanson *et al.* (75)	2007	122	Surgery	8			28			PSA ≤ 0.4
Abdollah *et al.* (76)	2015	1100	Surgery	1			50			PSA ≤ 0.2
Joniau *et al.* (55)	2014	1360	Surgery	43			55			PSA ≤ 0.2
Briganti *et al.* (77)	2012	1366	Surgery	30			54			PSA ≤ 0.2
Yamamoto *et al.* (78)	2012	378	Surgery	0			49			PSA ≤ 0.2
Loeb *et al.* (79)	2010	175	Surgery	0			68			PSA ≤ 0.2
Inman *et al.* (80)	2008	236	Surgery	59			39			PSA ≤ 0.2
Bastian *et al.* (81)	2006	220	Surgery	0			27			PSA ≤ 0.2
Ward *et al.* (82)	2005	841	Surgery	51			43			PSA ≤ 0.2

ADT = androgen deprivation therapy; LDR = low dose rate; EBRT = external beam radiation therapy; PSA = prostate-specific antigen; HDR = high dose rate; RT = radiation therapy.

both high-risk and unfavorable intermediate-risk prostate cancer. Patients were randomized to receive either dose-escalated EBRT to 78 Gy or a combination of EBRT to 46 Gy followed by an ^{125}I LDR boost. All of the patients received 1 year of ADT. This trial differs from the two earlier randomized trials in that the earlier trials enrolled fewer patients, included patients with more favorable disease, employed variable use of ADT, and used lower radiation doses than what is accepted in the contemporary age. Approximately 70% of the patients on ASCENDE-RT had high-risk disease ($n = 276$). Early results of this trial with a median followup of 6.5 years have been reported and show a striking benefit in bRFS with combination therapy. Given some controversy of the optimal definition of bRFS, this parameter has been reported both in terms of the surgical definition (PSA < 0.2) allowing appropriate comparison with surgical series and in terms of the Phoenix definition (PSA < nadir +2) allowing comparison with other radiation series. By the surgical definition of bRFS, there was an absolute difference of 51% at 9 years between the LDR-combination arm and the EBRT-alone arm (82.2% vs. 31.5%, $p < 0.0001$) (84). In the 276 high-risk patients, the absolute benefit of an LDR boost for bRFS at 9 years by the Phoenix definition was 20% (78% vs. 58%, $p = 0.05$) (59). A summary of the three randomized trials comparing combination therapy to EBRT can be found in Table 2.

It is important to note that the duration of ADT in both the prospective and retrospective series discussed typically

Table 2
Phase III clinical trials of EBRT vs. EBRT plus brachytherapy

Authors	Year	*N*	Median followup	Risk groups	Outcomes		
					EBRT	Combo	Significance
Sathya *et al.* (83)	2005	104	8.2 years	Low: 0% Intermediate: 40% High: 60%	5 yr bRFS: 39% Post-tx biopsy positive: 51%	71% 24%	SS SS
Hoskin *et al.* (40)	2012	218	7.1 years	Low: 5% Intermediate: 42% High: 53%	7-yr bRFS 48%	66%	SS
ASCENDE-RT (59)	2015	398	6.5 years	Low: 0% Intermediate: 31% High: 69%	9-yr bRFS 58%	78%	SS

EBRT = external beam radiation therapy; bRFS = biochemical recurrence-free survival; SS = statistically significant.

ranges less than the 2–3 years that is recommended with external beam radiation. The value of ADT has been reviewed retrospectively and has often not shown a benefit in the setting of a brachytherapy boost (85). However, retrospective comparisons are subject to selection bias, as often men at highest risk of progression are given ADT. At this time, it is difficult to define a subpopulation of high-risk patients in which ADT can be routinely omitted and it remains a component of standard of care. Additional studies are required to determine the optimal duration of ADT with CMRT, and we would recommend a minimum of 1 year based on the results from ASCEND-RT.

Although biochemical recurrence has typically been viewed as a poor surrogate for overall survival for prostate cancer patients as a whole, in high and very high-risk patients, biochemical recurrence is closely linked to the need for salvage therapies which can greatly impact quality of life in the short term and progress to lethal disease in a significant proportion of failures. The impact of primary treatment on overall survival is often disguised by the use of salvage ADT as there can be a long duration of response to salvage ADT, with a median time to castration-resistant disease of 7 years after radiotherapy. However, salvage ADT and other systemic therapies have significant side effects. Therefore, patients must be fully informed of their risk of recurrence and their likelihood of needing future treatment and their associated side effects and potential impact on quality of life. In the era of shared decision making, all patients should have an informed discussion of the benefits of combination therapy approaches.

Combined modality toxicity

The goal of treatment is both cure and quality of life preservation, including urinary function and sexual quality of life. Perhaps the strongest criticism of ASCENDE-RT is the high rate of late Grade 3 GU toxicity including urinary strictures with brachytherapy. Cumulative incidence of late Grade 3 GU toxicity in the brachytherapy arm was 18.4% compared to 5.2% in the external beam arm ($p < 0.0001$). Half of these complications were urethral strictures. However, there is little correlation between urethral stricture and dose to the prostate in their cohort. Instead, the ASCENDE-RT trialists acknowledge that there were flaws in their implantation technique, including overestimation of the apex and PTV margin further extending into the GU diaphragm, which is the more likely explanation for their toxicity (59, 84). Many of these complications did subside over time and the prevalence of Grade 3 GU toxicity at 5 years reduced to 8.6% in the brachytherapy arm compared to 2.2% in the EBRT-alone arm. In a separate series from the British Columbia Cancer Agency, Chan *et al.* demonstrated that brachytherapy-associated toxicity decreases with increasing experience. In a cohort of 2011 patients who underwent LDR brachytherapy, the rate of RTOG Grade 3 urinary toxicity dropped from 16.8% in the first 500 patients to 2.8% in the last 500 patients (86). These results reinforce that toxicity rates can be reduced over time as centers gain experience to optimize patient selection, implant technique, and treatment planning.

Stock *et al.* published one of the largest series of prostate cancer patients undergoing brachytherapy with 2495 patients, 943 of which received external beam radiation as well. In their experience, although approximately 56% of the cohort had worsening GU symptoms immediately post-implant, the average increase in IPSS from baseline is only approximately 1.9 points after 12 years of followup. Only 10% of their study population had experienced any degree or duration of urinary retention, and the majority of these were acute and short term. There was an association between pretreatment IPSS and urinary retention (60). These investigators have also reported long-term toxicity data on a unique group of men younger than age 60 years who were treated with LDR brachytherapy with or without external beam. In this cohort of 131 patients, Grade 3 GU toxicity occurred in only 4 (3%) patients at a median followup of 11.5 years, all of which were from urinary retention. No significant differences were found between patients who had an implant alone vs. an implant plus EBRT (87).

Modern retrospective reviews utilizing HDR brachytherapy have reported similar rates of late Grade 3 GU toxicity ranging from 1% to 14% (88).

Spratt *et al.* analyzed 870 intermediate-risk prostate cancer patients receiving either dose-escalated IMRT to 86.4 Gy or IMRT plus brachytherapy. The authors found that combination therapy resulted in improved biochemical control and distant metastases-free survival. Furthermore, they found that the 7-year actuarial late toxicity rates for Grade 2 gastrointestinal toxicity were 4.6% vs. 4.1% ($p = 0.89$), for Grade 3 gastrointestinal toxicity 0.4% vs. 1.4% ($p = 0.36$), for Grade 2 GU toxicity 19.4% vs. 21.2% ($p = 0.14$), and Grade 3 GU toxicity 3.1% vs. 1.4% ($p = 0.74$) for the IMRT vs. IMRT plus brachytherapy, respectively (8).

Multiple retrospective series have shown that combination therapy results in high rates of ED. However, three large series suggest greater toxicity is not inevitable with combination therapy. Spratt *et al.* (8) reported that there were similar rates of long-term sexual function between IMRT and IMRT plus brachytherapy (mixture of LDR and HDR) with 57.8% of men in the IMRT-alone group and 55.0% in the combination group retaining full potency ($p = 0.67$). Merrick *et al.* (89) reported a dramatic decrease in ED in a large retrospective series when dose was restricted to the penile bulb and infraprostate tissues (90). McLaughlin recently reported no difference in ED at 5 years post–dose-escalated external beam radiotherapy compared to combination therapy when vessel-sparing radiation was employed (91–93). Both series suggest that dose restriction to critical adjacent structures may allow high cure rates and quality of life preservation. The argument against combination therapy is often rooted in the increased rates of GU and sexual toxicity that have been reported in older studies or in ongoing studies that began accruing patients several years ago. As experience with prostate brachytherapy continues to build, imaging and technology improve, and patient selection criteria become more refined, it will become more commonplace to achieve high cure rates without increase in toxicity.

Combined modality vs. surgery

It has proven to be very challenging to compare radiation results to surgical results in high-risk patients. The two modalities have never been compared in a prospective randomized trial. The rationale for surgery in high-risk patients is not based on excellent results that stand alone, but rather based on comparisons with relatively ineffective beam-only radiation (94–98). Certain studies have suggested improved survival with prostatectomy; however, very few studies have compared "good surgery" to "good radiation" in the era of dose escalation, image guidance, and in conjunction with long-term ADT. Furthermore, the publications that have compared surgery favorably to EBRT are often plagued by differences in patient selection for both modalities and differences in preoperative vs. postoperative staging. These biased studies have even been meta-analyzed by Wallis *et al.* (99), and the results unsurprisingly and inaccurately demonstrate that surgery results in improved survival compared to radiotherapy-treated patients. Ultimately, retrospectively comparing these groups continues to lead to a "self-fulfilling prophecy." It is clear that surgical patients and radiation patients are different (radiation patients are older, have more comorbidities, and worse prognostic features), and there are too many unaccounted for variables to correct for on a multivariable analysis or matched pair analysis with propensity scoring. Additionally, variations in the definition of failure, followup, use of salvage therapies, and duration and use of ADT further confound these analyses. Thus, any nonrandomized comparisons will continue to lead to the unavoidable and false self-fulfilling prophecy that surgery yields improved outcomes over radiotherapy.

To elicit an unbiased understanding of contemporary surgical outcomes in patients with high-risk prostate cancer, we performed an extensive literature review of surgical series that focused strictly on clinically staged patients treated primarily with surgery alone (Table 1). Thirteen articles were identified that reported surgical outcomes on clinically staged high-risk patients. Rates of bRFS at 10 year ranged from 27% to 55% (14,55,76–82,100–102). This is consistent with the results from commonly used nomograms, such as the Memorial Sloan Kettering Nomogram. In a recent publication, Abdollah *et al.* (76) sought to better delineate this spectrum. This modern era paper reports long-term outcomes of 1100 high-risk patients treated with robotic prostatectomies with or without pelvic lymph node dissections at tertiary centers between 2002 and 2013. Approximately 50% of these patients had a clinical stage of T2a or less, and 70% had a PSA of 10 or less, which comprises a favorable high-risk population. Less than 5% received adjuvant treatment with either radiation or hormone therapy. BRFS in the cohort overall at 10 years was 50%, and clinical recurrence-free survival at 10 years was 87%. In those patients with a GS of 8 or greater and a PSA of 10 or less, bRFS averaged 36% and clinical recurrence-free survival averaged 85%. Recently, Kishan *et al.* published a multi-institutional analysis comparing outcomes in 487 patients with Gleason 9–10 disease treated with EBRT, CMRT, or Surgery. The patients managed with radiation were older, with higher PSAs, and higher clinical stage. Of the surgical patients, 12% received adjuvant radiation. The 10-year DMFS was highest in the CMRT patients at 90% compared to 67% for EBRT ($p = 0.0008$) patients and 62% for surgery patients ($p = 0.0003$) (103).

A direct comparison of surgery followed by adjuvant radiotherapy to combination brachytherapy is necessary to determine the optimal treatment paradigm for achieving the best cure rate and preserving quality of life. However, until such a study is done and until adjuvant radiation is regularly implemented after surgery for high-risk prostate cancer patients, the current state of evidence suggests that brachytherapy-based combination therapy provides the most durable control of disease.

Conclusions

The most common site of failure for men with high-risk disease treated with external beam radiotherapy is local (104). In multiple contexts, the intensification of local therapy (adjuvant radiotherapy after surgery or radiosensitization to improve local control with ADT) has demonstrated reductions in distant metastases and improvements in overall survival. Recently, the ASCENDE-RT study has shown impressive biochemical control benefits with the addition of a third way to intensify local therapy—the addition of a brachytherapy boost to external beam radiotherapy. Although followup is short, it is highly plausible that comparable benefits will be seen in distant metastases and overall survival as this trial matures.

Just as the use of adjuvant radiotherapy or ADT results in incrementally increased side effects, and early declines in quality of life, the addition of supplemental brachytherapy has also shown incremental increase in side effects. However, brachytherapy is highly operator dependent, and excellent quality of life outcomes have been demonstrated from high-quality implants using modern imaging and treatment planning techniques. Future comparisons of surgical outcomes and radiotherapy must include men treated with combination therapy instead of the current practice of comparing surgery with external beam often without ADT. Given the high recurrence rate after surgery alone or external beam radiotherapy alone for men with high-risk prostate cancer, the use of ADT and the strong consideration for the addition of brachytherapy should be viewed as the gold standard treatment approach today.

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